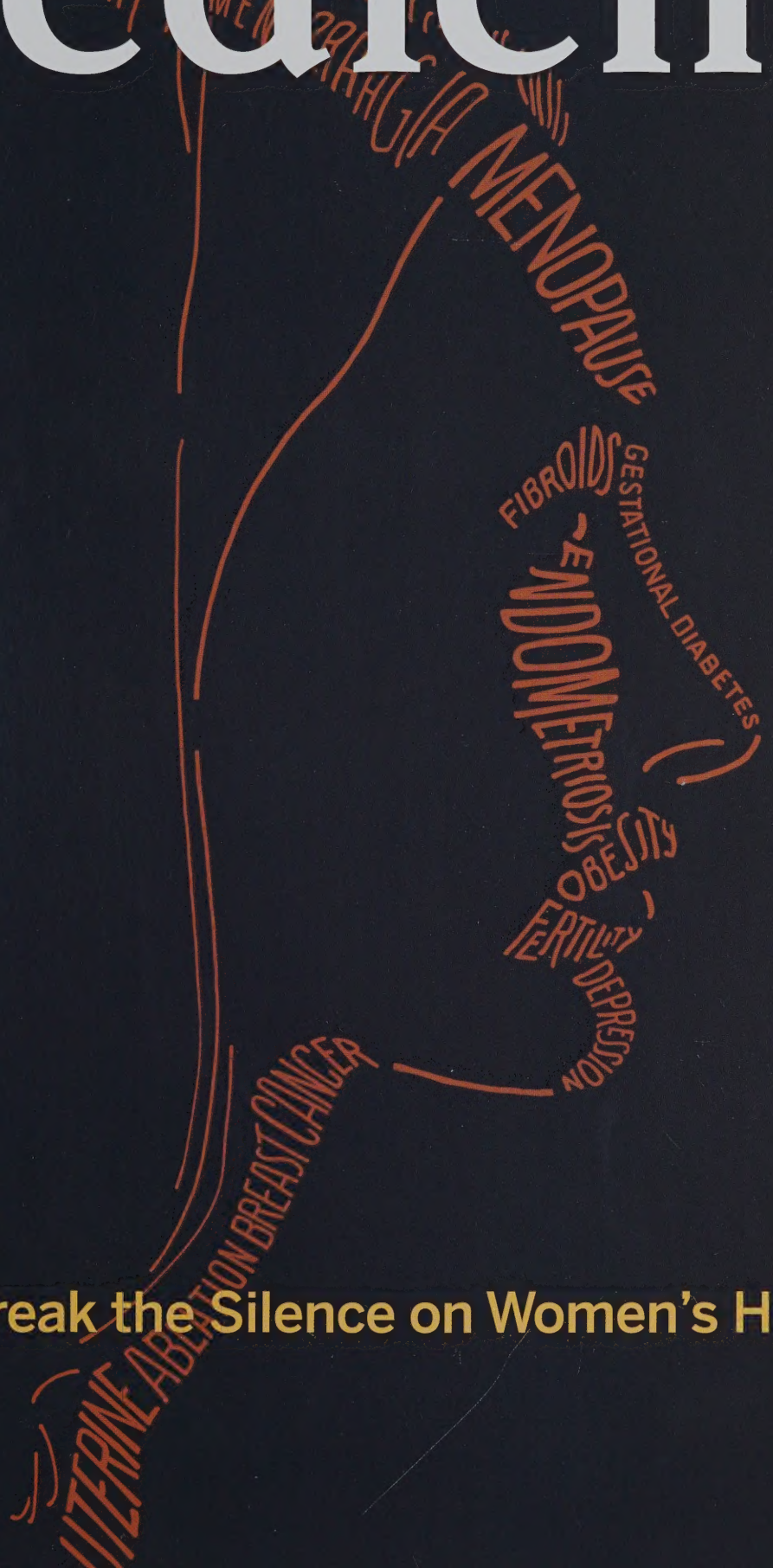
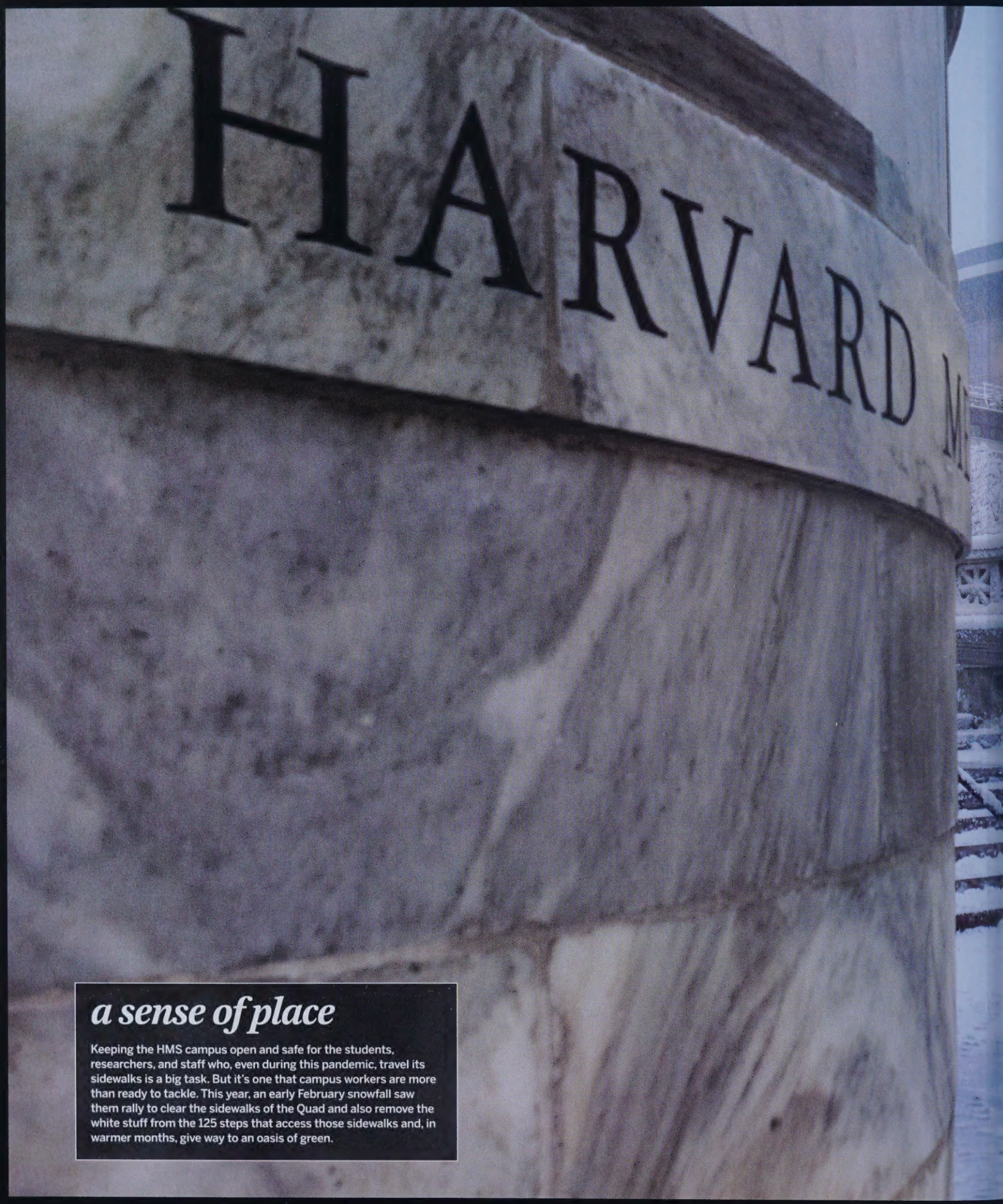
HARVARD
medicine
SPRING 2021

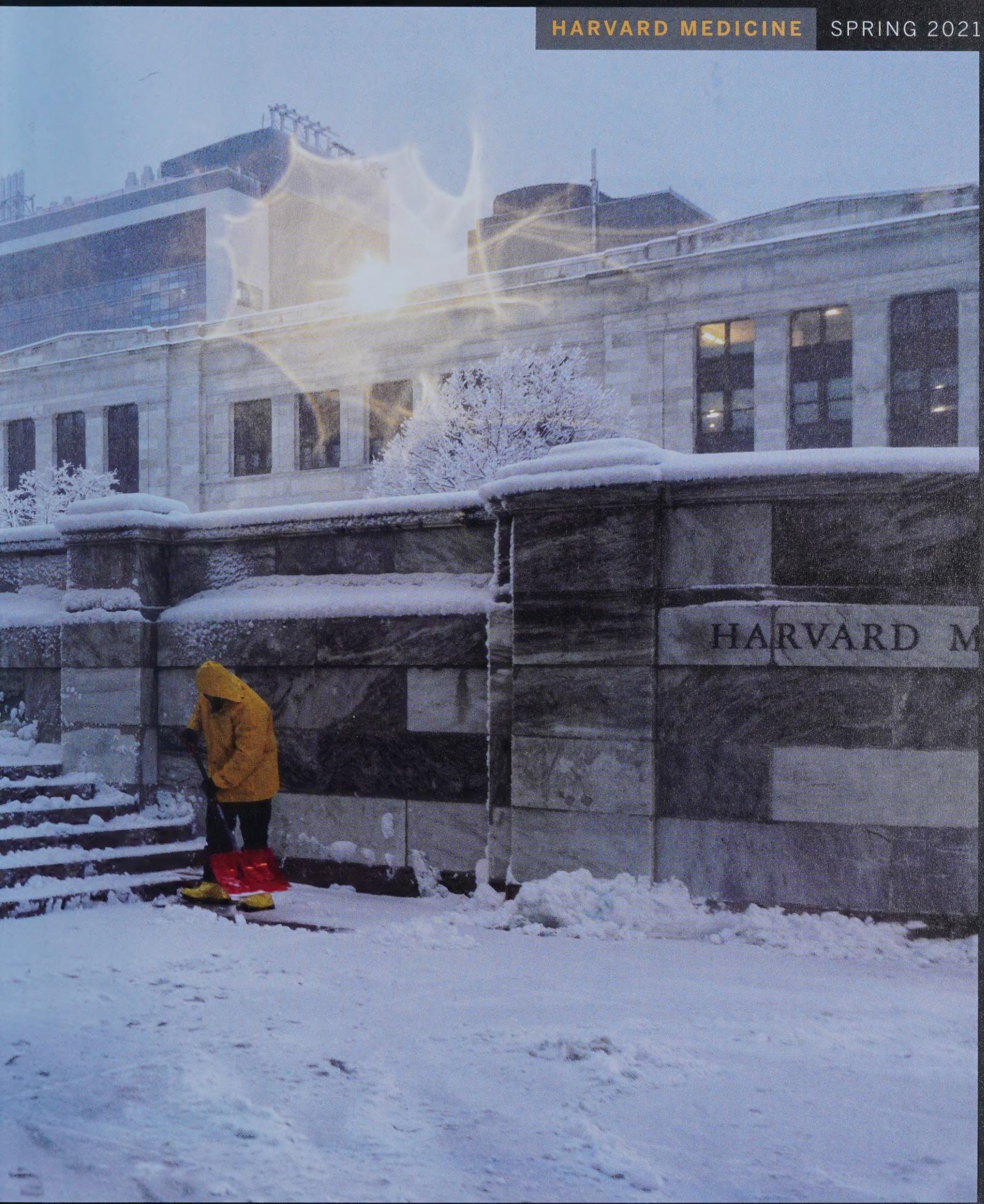


Let's Break the Silence on Women's Health



a sense of place

Keeping the HMS campus open and safe for the students, researchers, and staff who, even during this pandemic, travel its sidewalks is a big task. But it's one that campus workers are more than ready to tackle. This year, an early February snowfall saw them rally to clear the sidewalks of the Quad and also remove the white stuff from the 125 steps that access those sidewalks and, in warmer months, give way to an oasis of green.


HARVARD M

p. 44

IN MOTION: Shivangi Goel, an MD candidate, hopes to combine her clinical skills with her engineering acumen to develop medical technology that will make health care better and more accessible for all.

MATTIAS PALUDI (COVER); KELLY DAVIDSON (FACING PAGE)

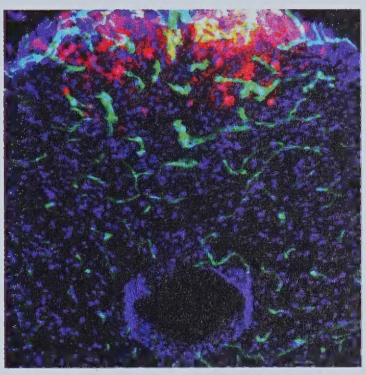
contents

Spring 2021 | Volume 94 | Number 2

SPECIAL REPORT
WOMEN'S HEALTH

FEATURE

DEPARTMENTS



p. 7

p. 28

p. 34

Women's health affects us all

ACCORDING TO THE WORLD HEALTH ORGANIZATION, a woman's lifetime risk of maternal mortality is 1 in 5,400 in high-income countries, yet 1 in 45 in low-income nations. In the United States, the numbers are also troubling, especially for some groups. In January 2020 the U.S. Centers for Disease Control and Prevention reported that throughout the previous decade, slightly more than 17 maternal deaths occurred per 100,000 live births. Among non-Hispanic Black women, however, there were 37 deaths per 100,000 births while among women over age 40, the rate approached 82 per 100,000. Unfortunately, these reported numbers may be underestimates: It wasn't until 2017 that all states offered a way to indicate maternal death on death certificates.

It is inexplicable that in the twenty-first century fundamental physiological processes such as pregnancy and childbirth are causing so much damage and death. Or that each year, vast numbers of women worldwide suffer and die not only from sexual and reproductive disorders but increasingly from noncommunicable diseases such as musculoskeletal disorders, cardiovascular disease, diabetes, and depression. The toll is great while our knowledge of how to help remains comparatively minuscule.

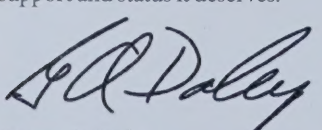
For decades, the percentage of women in our entering classes has been increasing. In 2020, women comprised 60 percent of our incoming class.

Women have long called for attention to these matters. Fortunately, those calls are increasing, demanding better clinical interventions and more research, particularly calls for including women as participants in all research and requiring explicit justification for any exclusion. And fortunately, the physicians and scientists in the HMS community are responding to these calls.

Many of our alumnae and faculty have been changing how medicine cares for women. In 1985, for example, Karen Carlson, MD '80, founded Women's Health Associates at Massachusetts General Hospital, a multidisciplinary women's health practice that became a model for several National Centers of Excellence in Women's Health established throughout this country. In 1989, anesthesiologist Nancy Oriol, MD '79, developed what is known as the walking epidural, an anesthetic technique that allows laboring women to move and one that she introduced to China in 2002 as a possible solution to that country's high elective cesarean rate. And for the past few decades, Karol Watson, MD '89, a renowned cardiologist and guiding hand at the UCLA Barbra Streisand Women's Heart Health Program, has helped advance our understanding of heart disease in all women.

Another encouraging sign of change: the composition of our student body. For several decades the percentage of women in our entering student classes has been steadily increasing. In 2020, women comprised 60 percent of our incoming class. This growth is especially encouraging since research increasingly indicates that gender concordance in care improves patients' perception and outcomes.

There is still much to do. But we can be assured that the intelligence and talent of our alumni and our faculty will continue to drive change so that women's health achieves the support and status it deserves.



George Q. Daley
Dean of Harvard Medical School

HARVARD medicine

Editor
Ann Marie Menting

Design Director
Paul DiMattia

Associate Editor
Susan Karcz

Designer
Maya Rucinski-Szwec

Contributors
Jessica Cerretani; Stephanie Dutchen; Elizabeth Garner; Elizabeth Gehrman; Dominic Hall; JiYeon Kim; Ekaterina Pesheva

Harvard Medicine is published three times a year at 25 Shattuck Street, Boston, MA 02115.

PUBLISHERS: Harvard Medical Alumni Association and Harvard Medical School

PHONE: 617-432-7878
EMAIL: harvardmedicine@hms.harvard.edu
MAIL: 107 Ave. Louis Pasteur, Boston, MA 02115
WEB: hms.harvard.edu/magazine
ISSN 2152-9957 | Printed in the U.S.A.

RANDY GLASS

Now is the time

It was with relief and sadness that I read the Winter 2021 edition of *Harvard Medicine* from cover to cover. I am grateful that you are finally telling these stories and truths, and I am deeply sad that it has taken so long. I graduated in 1994 and, perhaps like many others, I have carried similar memories for years, held close to the vest.

In particular, I remember egregious things we were taught about women and especially about women of color. These stigmatizing and false claims were horrifying to me at the time, and they drove me into a career in OB-GYN, public health, and health administration. They also defined my mission: Whenever I have heard explanatory frameworks that blame people and populations for their poor health outcomes, I have turned the spotlight onto the health care system to identify and address the ways in which *we* are creating the problem.

Some of the most offensive claims were embedded in our textbooks. Over the decades I have carried an armload with me from home to home so that I would have "evidence" if I was ever asked to back up my memories. Finally, in the past year, I got rid of those books but ripped out and kept the culprit pages so that I may still have them available.

I dearly hope that this journey of truth and reconciliation is not a short-lived fad. We have so much more work to do.

KATHERINE JAHNIGE MATHEWS, MD '94
ST. LOUIS, MISSOURI

Ties that bind

Confronting Racism in Medicine, the theme of your Winter 2021 issue, brought to remembrance the year my husband, James W. Forrester, MD '53, applied to HMS. He was being separated from the U.S. Navy and had had no pre-med at the Naval Academy. One day, while in Boston, he decided to visit HMS and inquire about applying. While talking to a secretary, Jim recalled she observed, "There's Dr. Dunphy walking on the campus. Why don't you talk to him?" And my husband did. As they parted Dr. Dunphy called to him, "Forrester, why do you want to be a doctor?" Jim answered without hesitation, "because I want to return to the South [South Carolina] to try to make health care better for the Blacks." And he did that as a surgeon for over fifty years. He felt his reponse might have been instrumental in his acceptance.

Fifty years later, a person came to our home to assist with an electrical problem. He introduced himself with the last name Dunphy. I told him about a Dr. Dunphy who my husband admired greatly. He said, "That was my grandfather."

J. Englebert Dunphy, MD '33, had a special feel for the underprivileged and the military because he himself had had a needful childhood.

ELIZABETH L. FORRESTER
SAVANNAH, GEORGIA

Speak up for science

This past year, 2020, has been unlike anything we could have anticipated when we entered HMS and launched ourselves into our careers in medicine. We expected, and have seen, ongoing enormous progress in the basic sciences and in the clinical practices underlying all the different pathways we and our classmates have followed. In addition to its scientific aspects, the COVID-19 pandemic has added an element that none of us could have envisioned in terms of its societal impact.

One of the most important changes we have witnessed in the decades since graduating has been the development and role of evidence-based medicine, relying on scientific methodology as it applies to clinical practice. Clinical impressions and observations continue to provide important insights. These are now assessed through appropriately designed clinical trials, as a way to validate, and sometimes invalidate, initial clinical impressions.

There is an ethical obligation for each of us to recognize the influence we have as physicians through our stature in the broader community. We have, unfortunately, seen a number of physicians use their positions to push unvalidated approaches in public forums: As a group, all alumni need to speak out against such behavior. Both through our medical societies and our academic institutions, we should not condone or tolerate physicians who knowingly ignore the current scientific evidence and use their positions to spread disinformation. The negative consequences are very real when the broader community relies on unsupported or disproven information and ignores validated approaches to halting the pandemic.

MICHAEL ROSS, MD '70
DEDHAM, MASSACHUSETTS
MITCHELL ROSS, MD '97
PARADISE VALLEY, ARIZONA

When we went to press with the Winter 2021 edition of *Harvard Medicine*, the photo we featured at the beginning of Rounds (left) identified two of the three individuals in the picture. Try as we might, we could not determine the name of the medical student on the far left of the photo. Fortunately, a sharp-eyed reader sent us a note, suggesting the person we had identified as "another HMS student" might well be Benjamin Medoff, MD '94. So, we contacted Medoff.

"Yes, that is me," the doctor kindly acknowledged.

Mystery solved (and editors cheer)!

Future vision

I enjoyed reading the "Field Correction" article from your Winter 2021 issue on confronting racism in medicine. It reminded me of six decades of interactions with doctors (other than my father, who was a general practitioner and general surgeon back in the days when that was possible).

Even being white and male, I've had to fight constantly to explain my individual medical characteristics, e.g., unusually low pain threshold. I look forward to the day when instant DNA analysis, etc., can provide my personal, individual profile for use in diagnostics.

As I read the article and eliminated from my mind the issue of race and skin color, I found it described precisely my own experience in obtaining medical care.

I was also pleased to note that the article did not deny that race exists or that there are racial characteristics that should be taken into account by physicians. As the article makes clear, much more research needs to be done on these issues.

For me, the article explained the problems that arise generally from putting patients into pigeonholes. How wonderful it will be when data can be analyzed to permit truly individualized diagnosis and care. I hope I live long enough to see definitive results.

I personally have always celebrated racial and cultural diversity and wouldn't want to live in a world without such differences.

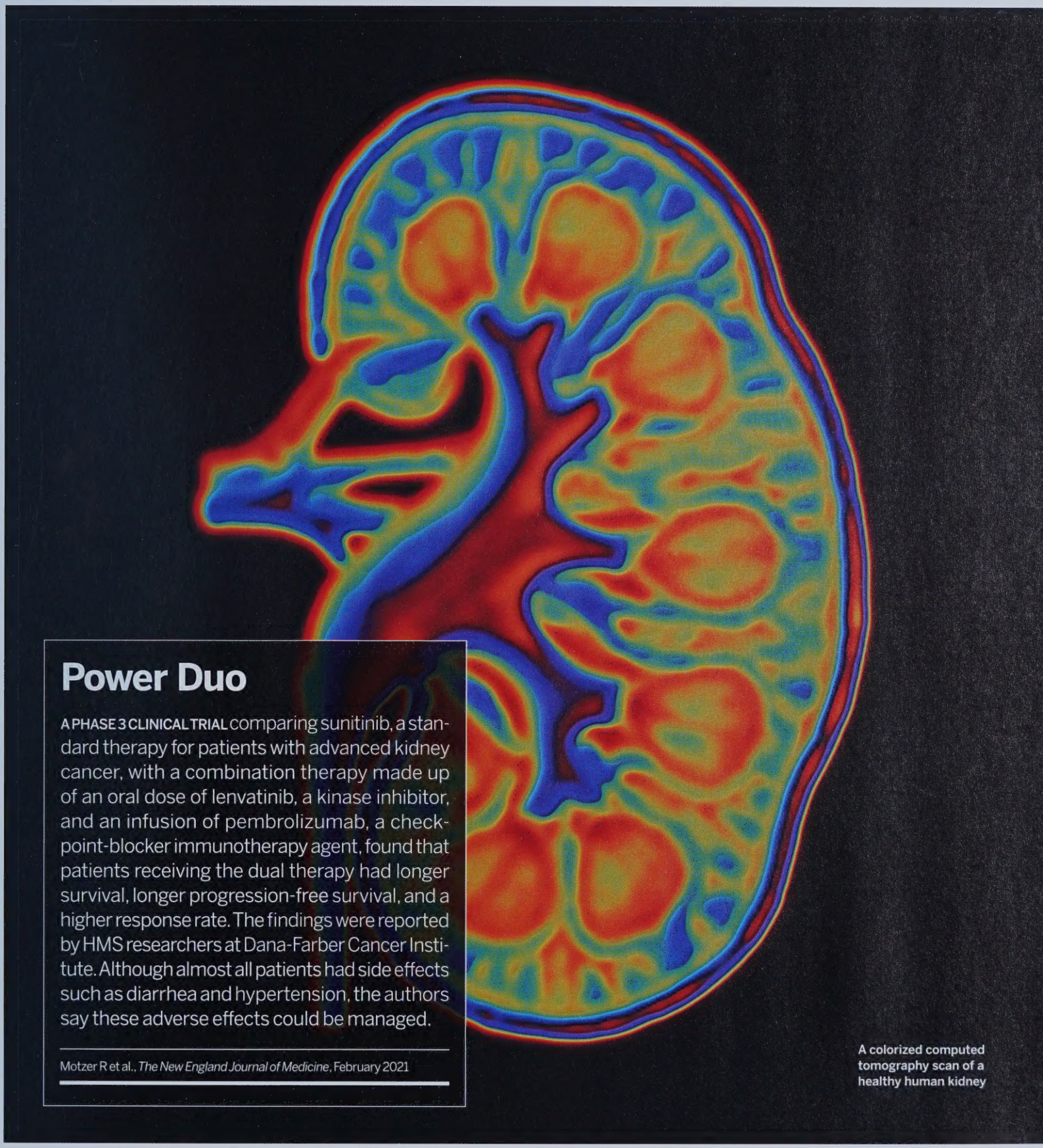
Thanks for publishing the article and thanks to the *Harvard Gazette* for bringing it to my attention.

BRUCE HENDERSON
SAN DIEGO, CALIFORNIA

Say it ain't so

After reading the article "Field Correction" in the Winter 2021 issue of *Harvard Medicine*, my mood sank, and a wave of pessimism invaded my brain. I understand the need to change the preconceived ideas that some doctors may have while caring for minority patients. But, really! It is not as bad as your article describes. It is an exaggerated way to drive the need for improving the care of all races. I am a medical doctor who was shocked by reading your lines after 37 years in practice.

SEVI AVIGDOR
RUMSON, NEW JERSEY



Power Duo

A PHASE 3 CLINICAL TRIAL comparing sunitinib, a standard therapy for patients with advanced kidney cancer, with a combination therapy made up of an oral dose of lenvatinib, a kinase inhibitor, and an infusion of pembrolizumab, a checkpoint-blocker immunotherapy agent, found that patients receiving the dual therapy had longer survival, longer progression-free survival, and a higher response rate. The findings were reported by HMS researchers at Dana-Farber Cancer Institute. Although almost all patients had side effects such as diarrhea and hypertension, the authors say these adverse effects could be managed.

Motzer R et al., *The New England Journal of Medicine*, February 2021

A colorized computed tomography scan of a healthy human kidney

ALFRED PASIEKA/SCIENCE SOURCE

I Heart Microbes

AN INTERNATIONAL STUDY involving HMS researchers at Massachusetts General Hospital has found that a diet rich in plant-based foods is linked with an abundance of gut microbes associated with a lower risk of developing conditions such as obesity, type 2 diabetes, and cardiovascular disease. The microbiome-based biomarkers for obesity as well as markers for cardiovascular disease and impaired glucose tolerance were so robust and consistent that the investigators say their microbiome data can be used to determine the risk of cardiometabolic disease among asymptomatic people and, possibly, to develop personalized therapeutic diets.

Asnicar F, Berry S et al., *Nature Medicine*, January 2021

CARLOSGAWE+/GETTY IMAGES

CARDIOLOGY

Time of exercise matters for men with diabetes

ALTHOUGH MANY STUDIES HAVE SHOWN that physical activity improves heart health in patients with type 2 diabetes, few have considered whether exercising at a certain time of day provides an extra health benefit for this population. Now, a study by HMS investigators at Joslin Diabetes Center and Brigham and Women's Hospital, along with collaborators, gives insight, reporting a correlation between the timing of moderate-to-vigorous physical activity and cardiorespiratory fitness and health risks in individuals who have type 2 diabetes and who are obese or overweight.

When the researchers analyzed data on more than 2,000 people, they found that men who have type 2 diabetes or are obese or overweight and exercise in the morning had higher cardiorespiratory fitness compared with men with these conditions who are most active midday. The findings were independent of the amount and intensity of weekly physical activity. Notably, men with these conditions who exercise in the morning also had a higher chance of developing coronary heart disease in the next four years than individuals in all other exercise groups.

For women, no link between the timing of physical activity and coronary heart disease risk or cardiorespiratory fitness was found.

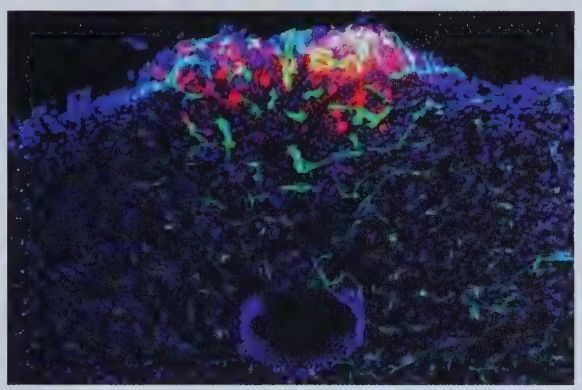
Sex-specific physiological differences may help explain the more prominent correlations seen in men, who tend to be at risk of coronary heart disease earlier in life. However, the researchers note that other factors could be at play, such as the effect the circadian system has on time-specific physical activity.

The researchers, for example, could not account for participants' varying circadian rhythms: a jog at 6 p.m. for one participant may be "evening exercise" while for another participant who wakes later in the day, it may biologically be "afternoon exercise." There is a growing interest in the interaction between physical activity and the circadian system, according to the researchers.

Qian J et al., *Diabetes Care*, February 2021

Cell Biology

Neurons that mediate nausea-like behavior identified



CHUCHU ZHANG STEPHEN LIBERLES

In research on the neural mechanisms mediating nausea-like behaviors, HMS cell biologists have identified and characterized neurons involved in regulating these responses in a mouse model. The neurons are found in the brain stem's area postrema, which, because of its location outside the blood-brain barrier, can detect toxic chemicals and other potentially harmful blood-borne substances. The findings could lead to improved anti-nausea medications that would benefit patients who experience severe, even life-threatening, nausea during chemotherapy regimens.

Zhang C et al., *Neuron*, December 2020

GERONTOLOGY

Biomarker for postoperative delirium identified

AN INTERDISCIPLINARY TEAM of HMS researchers at Beth Israel Deaconess Medical Center has identified a single protein present in the blood that is associated with increased risk of postoperative delirium. The finding sheds light on a potential pathophysiological mechanism underlying delirium and paves the way for a noninvasive, cost-effective test to guide prediction, diagnosis, and monitoring of delirium. Preoperative blood tests for these proteins could help physicians determine which patients are at higher risk for developing this form of confusion.

Delirium, a common syndrome among older adults, is a form of acute confusion that is characterized by poor attention, disorientation, impaired memory, delusions, and abrupt changes in mood and behavior, particularly in critically ill patients in the ICU, in older patients with multiple health issues, and in those who have recently undergone surgery. Patients who experience delirium are also at increased risk of long-term cognitive decline.

Despite its pervasiveness, delirium has remained a clinical diagnosis with no established diagnostic tests. The team notes that the discovery of a reliable biomarker could change that.

For the study, the researchers analyzed more than 1,300 proteins in blood samples from participants in the Successful Aging after Elective Surgery study, which investigates the long-term outcomes and novel risk factors for delirium after surgery or hospitalization in older adults. They found that a single protein, known as chitinase-3-like-protein-1, was present at higher concentrations in the blood both before and after surgery in patients who experienced delirium compared with patients who did not develop postoperative delirium. This protein is also linked to aging and age-related conditions, including Alzheimer's disease, and plays a critical role in the body's type 2 immune response.

In addition, the team found that patients who had high preoperative levels of the protein as well as high postoperative levels of an immune-related protein called interleukin-6 were at increased risk of delirium.

The findings add to other research that suggests a link between delirium, aging, and Alzheimer's disease.

Vasunilashorn SM et al., *Journal of Gerontology: Medical Sciences*, February 2021

NEUROLOGY

Telemedicine for strokes found to save lives

PATIENTS WHO GO TO THE HOSPITAL with symptoms suggestive of a stroke need rapid expert assessment and treatment to halt brain damage; it could mean the difference between life and death. Yet many hospitals do not have round-the-clock stroke care teams. To make up for this deficiency, many U.S. hospitals offer telemedicine consults with stroke specialists who may be located hundreds of miles away.

A study by health policy researchers in the Blavatnik Institute at Harvard Medical School and colleagues shows that patients who receive stroke care at facilities with telemedicine consults for stroke assessment, known as telestroke, receive better care and are more likely to survive strokes than patients who go to similar hospitals without these services. The study represents the first national analysis of telestroke patient outcomes.

The telestroke services evaluated in this study allow hospitals without local expertise to connect patients to neurologists who specialize in treating stroke. Off-site experts can examine by video an individual with symptoms suggestive of stroke, review brain imaging or radiology tests, and make recommendations about the best course of treatment.

One outcome the study looked at was whether patients received reperfusion treatment, which restores blood flow to regions of the brain affected by the stroke before irreparable damage occurs.

Compared with patients who received care at hospitals without telestroke, patients who received care at telestroke hospitals had 13 percent higher relative rates of reperfusion treatment and 4 percent lower relative rates of 30-day mortality. The researchers saw the largest benefits at smaller hospitals, at rural hospitals, and in patients 85 and older.

The researchers point out the benefits that telestroke would offer rural hospitals if it were made available, and if they had the budget for it, and note that the findings emphasize the need to address the financial barriers smaller hospitals face in introducing such services.

Wilcock A et al., *JAMA Neurology*, March 2021

CARDIOLOGY

Insulin resistance flags early heart disease risk

ALTHOUGH DEATHS RELATED TO HEART DISEASE have declined among older people, studies suggest that these deaths among younger patients have remained unchanged or have improved minimally in the past two decades.

To understand what puts younger individuals at higher risk of premature coronary heart disease, HMS researchers at Brigham and Women's Hospital and colleagues at the Mayo Clinic analyzed a set of risk factors in more than 28,000 female health professionals who had participated in a decades-long study and were without known cardiovascular disease. The research team found that women under the age of 55 with type 2 diabetes had a tenfold greater risk of having heart disease over the next two decades than older women and that lipoprotein insulin resistance was a strong predictive biomarker for developing the disease.

The researchers analyzed approximately 50 biomarkers associated with cardiovascular health, including commonly used metrics such as low-density lipoprotein cholesterol and hemoglobin A1C. These measures had much weaker associations with heart disease onset in women younger than 55 years than lipoprotein insulin resistance, a newer metric for insulin resistance that uses a weighted combination of six lipoprotein measures and is analyzed through specialized laboratory testing. Although low-density lipoprotein was associated with only a 40 percent increase in risk of coronary heart disease in women under 55, lipoprotein insulin resistance demonstrated a 600 percent risk increase.

The researchers found that in otherwise healthy women, insulin resistance, type 2 diabetes, and metabolic syndrome were major contributors to premature coronary events. Women under 55 who had obesity had about a fourfold greater risk for coronary events, as did women in that age group who smoked or had hypertension.

The researchers note that the study is limited in its generalizability because it focused on women, who have worse outcomes after premature cardiac events than men, and because 95 percent of its participants were white.

Dugani SB, Moorthy MV et al., *JAMA Cardiology*, January 2021

OBSTETRICS AND GYNECOLOGY

SARS-CoV-2 antibodies do not readily cross placenta

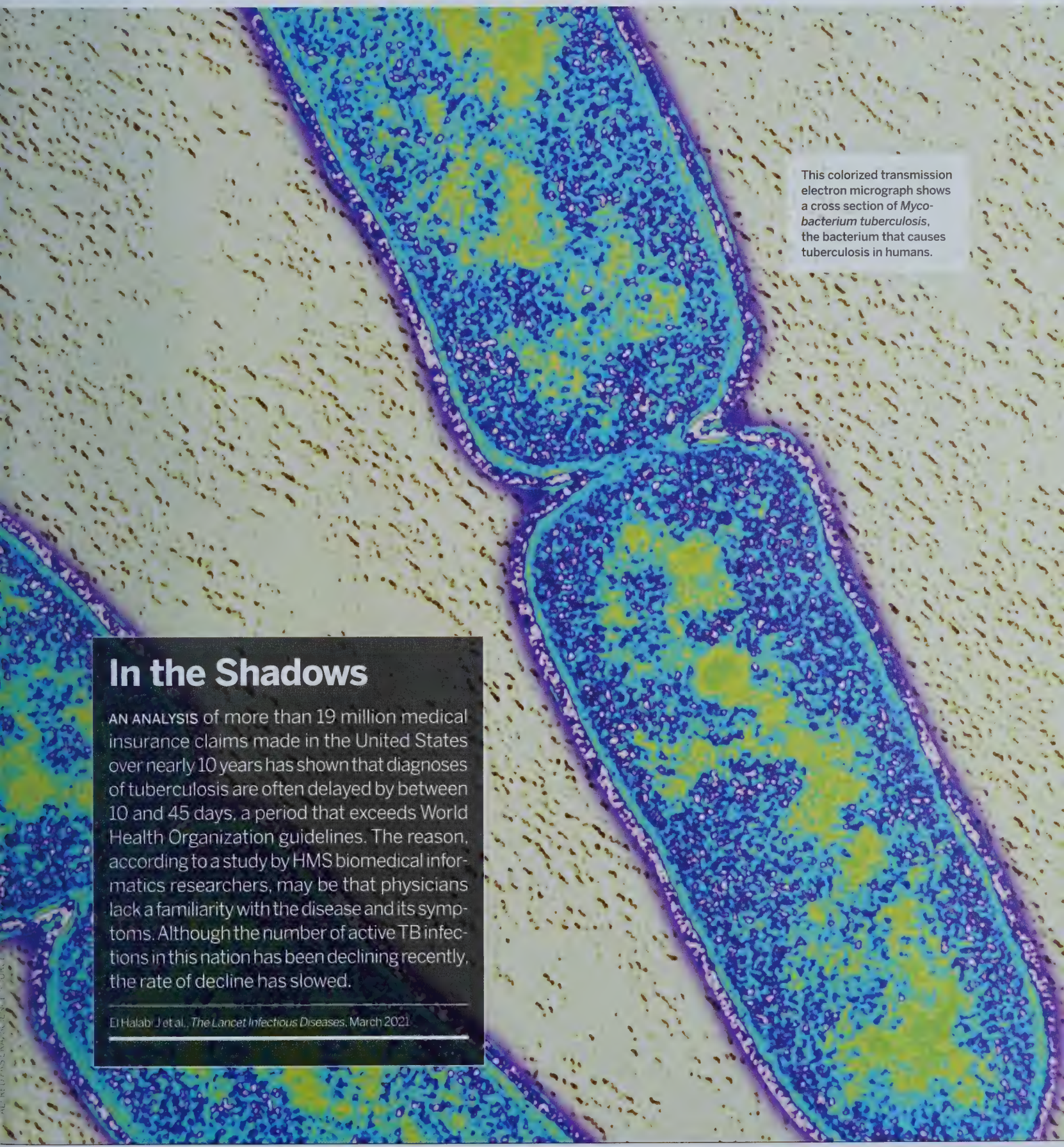
PREGNANCY INCREASES VULNERABILITY to developing severe cases of COVID-19 following SARS-CoV-2 infection, but little is known about the anti-SARS-CoV-2 immune response during pregnancy or how it may affect offspring. A study by HMS investigators at Massachusetts General Hospital provides insights that could inform care for infected women and their newborns.

The study included 127 pregnant women in their third trimester who received care at three Boston hospitals between April and June 2020. Among the 64 women who tested positive for SARS-CoV-2, investigators detected virus in their respiratory systems but did not detect virus in maternal or cord blood. There were no signs of the virus in placentas nor was there evidence of viral transmission to newborns. The researchers suspect that transmission to the fetus may be blocked because the mother's blood did not have the virus and because the major molecules used by SARS-CoV-2 to enter cells (ACE2 receptor and TMPRSS2 enzyme) are often not physically located together in the placenta.

Most of the participants who tested positive developed antibody responses against SARS-CoV-2 proteins. However, when researchers looked for the transfer of anti-SARS-CoV-2 antibodies to the newborn through the placenta, they found it was significantly lower than the comparative transplacental transfer of anti-influenza antibodies. Transplacental transfer of antibodies to the fetus is typically highest in the third trimester, yet the researchers found significantly reduced transfer of SARS-CoV-2 antibodies relative to levels typically found for influenza.

The low antibody transfer, the researchers say, highlights the need to consider the optimal timing of vaccine administration to best support maternal and newborn immunity.

Edlow AG et al., *JAMA Network Open*, December 2020



This colorized transmission electron micrograph shows a cross section of *Mycobacterium tuberculosis*, the bacterium that causes tuberculosis in humans.

In the Shadows

AN ANALYSIS of more than 19 million medical insurance claims made in the United States over nearly 10 years has shown that diagnoses of tuberculosis are often delayed by between 10 and 45 days, a period that exceeds World Health Organization guidelines. The reason, according to a study by HMS biomedical informatics researchers, may be that physicians lack a familiarity with the disease and its symptoms. Although the number of active TB infections in this nation has been declining recently, the rate of decline has slowed.

El Halabi J et al., *The Lancet Infectious Diseases*, March 2021

noteworthy

Education policies, programs reviewed for racism issues

In its effort to become a more inclusive, diverse, and anti-racist institution, in 2020 the HMS Program in Medical Education formed the PME Task Force to Address Racism to review and analyze policies and programs across PME and to offer concrete recommendations and possible solutions to areas identified as needing improvement.

The task force, co-chaired by Andrea Reid, MD '88, (*fig. 1*) HMS associate dean for student and multicultural affairs for PME, and Fidencio Saldaña, MD '01, HMS dean for students, and comprising 150 students, faculty, and staff, has been examining the School's learning environment, as well as the curriculum, faculty and staff development, admissions processes, assessment practices, and student affairs.

The task force is preparing to present its findings and recommendations to the School's Educational Policy and Curriculum Committee in April.

"This has been an incredible grassroots effort by many, many faculty and students, to take a hard, bottom-up look at every aspect of the MD program," said Edward Hundert, MD '84, HMS dean for medical education.

The task force's goal is to take a comprehensive approach to addressing a history of white supremacist culture at the School, he said, and HMS is not alone in this effort. HMS hospital affiliates, where HMS students train, have also launched their own anti-racism initiatives, and medical schools around the United States have been asking the same tough questions of their programs.

All involved with the PME task force are trying to determine what change or improvement is needed within their programs, making an effort to propose solutions that will create a more inclusive, welcoming environment at HMS, both on the Quad and at the hospitals.

"When we don't retain as many of our underrepresented students, as many of our Black students, in our own residencies, as we do our white students, we have a problem. We have to hold that up, address it, and work on it," said Hundert.

A renovated Countway Library reopens with the new year

Following extensive renovations that began in October 2019, the Francis A. Countway Library of Medicine reopened in early January (*fig. 2*), under the limits of current pandemic restrictions. The wide range of renovations will allow the library to offer a variety of adaptable spaces for individual and group study, event and multi-use instruction rooms, and a makerspace work area featuring a 3D anatomy and physiology visualization table.

One of the more notable changes is the new entrance opening on to Huntington Avenue, meant to offer more access to the building and to present a welcoming face to campus neighbors. Other changes include increased accessibility inside and outside the library, new exhibit and display locations, a first-floor café, a pop-up Harvard Coop, the addition of a mothers' room and a prayer/meditation room, and a greater number of restrooms for women, men, and all genders. In addition, the renovation opened the entire building to more natural light, a change that brought with it more views of the campus.

According to Elaine Martin, director and head librarian of the Countway, the renovations will help the library meet the demands of twenty-first-century scholarship.

"The health sciences, technology, and information environment is rapidly changing," said Martin. "To deliver on Countway's commitment to innovation, collaboration, academic excellence, improvements in technology, and diversity and inclusion, we aimed to create a fresh, adaptable, dynamic hub for members of the Longwood community."

Patrons' initial reactions to the renovations have been overwhelmingly positive, said Martin.

fig. 1

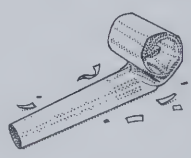


fig. 2

fig. 3

"The library reopening gives the Longwood community a new, refreshing, and positive environment in which to work, study, and research. And for that I am grateful."

HMS faculty to lead CDC, serve as science advisor

In late January, Rochelle Walensky, HMS professor of medicine, stepped into a new role: director of the U.S. Centers for Disease Control and Prevention. Walensky (*fig. 3*), who was also the chief of the Division of Infectious Diseases at Massachusetts General Hospital, is the CDC's nineteenth director and the ninth administrator of the Agency for Toxic Substances and Disease Registry, a federal public health agency within the U.S. Department of Health and Human Services.

Walensky takes over as head of the internationally recognized public health agency as the world continues to struggle with SARS-CoV-2 and the COVID-19 pandemic. While at HMS and Mass General, she served on the frontline of the pandemic and conducted research on vaccine delivery and strategies to reach underserved communities. She is nationally known for her work motivating health policy and informing clinical trial design and evaluation in various settings.

Her pioneering research on HIV and AIDS has helped advance the national and global response to that public health crisis while her expertise on the testing for and treatment of other deadly viruses has gained her international renown.

Walensky earned her MD from Johns Hopkins School of Medicine and her MPH from the Harvard T.H. Chan School of Public Health.

Another key role in the Biden administration, that of White House Science Advisor, has been filled by Eric Lander, founding director of the Broad Institute of MIT and Harvard, HMS professor of systems biology, and MIT professor of biology. A geneticist, molecular biologist, and mathematician, Lander is the first life scientist to serve in this role.

RANDY GLASS

To See Beyond

FOR NEARLY AS LONG as humans have expressed themselves through art, the female figure has been rendered. According to scholars, the Stargazer, the 5,000-year-old marble female figurine shown here, was produced by the ancient Cycladic culture, a civilization that, together with the Minoan and the Mycenaean cultures, prospered during the Aegean Bronze Age. The figurine gets its name from the upward cant of its head, seemingly looking to the stars. It is a posture of hope, yearning, promise, and possibility. It is an attitude that could also describe that of the experts we spoke with for this issue on women's health.

Transformations

Maggie Taylor
The alchemist's chamber
Digital composite
Limited edition inkjet print
22 x 22 in

MAGGIE TAYLOR

The mental health issues that can accompany menopause often go unaddressed

BY STEPHANIE DUTCHEN

VANESSA HAYGOOD, MD '78, remembers when the referrals started rolling in to her obstetrics and gynecology practice in Greensboro, North Carolina. What gave her pause wasn't that primary care physicians would send women in their forties and fifties to her with complaints of anxiety or depression. It was how often the accompanying notes indicated that the cause boiled down to "just menopause" and that the women simply "needed some hormones."

Thirty years of clinical experience taught Haygood what more clinicians and researchers appreciate with each passing year: that changes in mental health can indeed accompany the transition into menopause, sometimes with such intensity that they damage physical health, quality of life, relationships, and work, and that the causes are complex and the treatments many.

Yet the reductionist, even dismissive, tone of the referrals reflected broader trends in mainstream U.S. culture and in the medical profession about which populations and conditions deserve attention. Attempts to address changes in mood and mental health around the time of menopause suffer from an unholy trinity of neglect: the patients affected are mostly women and women's health isn't studied or treated as thoroughly as men's, the women are typically heading into older adulthood in a society that clings to youth, and the problems are psychological in a health care system disposed to prioritizing the physical.

As a result, many women and their care providers don't fully appreciate the risk of developing new, relapsed, or worsened mental health conditions as menopause approaches. Those who are aware may not know how best to treat the symptoms. And researchers have barely begun to quantify menopause-associated mood changes and mental illnesses, pinpoint their causes, and compare the effectiveness of treatments.

"More attention should be given to the mental health aspects of menopause," says obstetrician-gynecologist Laurie Green, MD '76. "Women are suffering in silence."

Haygood, who retired last year, appreciated the referrals because she felt she could legitimize patients' concerns and discuss options. She only wishes more women enjoyed such support. "I'd like to see this attitude that it's 'just menopause' change. It would be a real advancement in care."

Signs and signifiers

Clinicians, such as Laura Payne, an HMS assistant professor of psychology in the Department of Psychiatry at McLean Hospital, offer a quantitative way to understand the problem when they explain that the menopausal transition "is a vulnerable time for women in terms of mental health struggles."

Patients, such as British journalist Rose George, paint the qualitative picture. "I am one of the women of menopause, who struggle to understand why we feel such despair, why now we cry when before we didn't, why understanding what is left and what is right takes a fraction longer than it used to … I miss myself, the woman who didn't feel like this," George wrote in *The New York Review of Books* in 2018. For her, as for a subset of women, terms like "low mood" and "brain fog" fail to capture the extent to which natural menopause "doesn't feel natural. It feels like a derangement."

Menopause, defined as having had no periods for one year, represents one of life's rites of passage: a bookend to the onset of menstruation in adolescence, marking the

end of fertility and the beginning of a new stage of life. It can be a source of joy, relief, pride, or darker sentiments. While some sail through the gradual winding down of the reproductive system known as perimenopause with no trouble other than missed periods, most must navigate stormy waters for anywhere from a few months to more than a decade, often without a compass—or even a raincoat. Clinicians have no way to predict how long an individual's journey will take or how smoothly it will go.

Physical hallmarks such as hot flashes and night sweats, which strike about three-quarters of perimenopausal women, don't tell the whole story.

Mood swings turn familiar emotional rhythms into a pinball game. Risks of depression, anxiety, and alcohol and substance use rise. So may those for psychiatric illnesses: Many women with bipolar disorder or schizophrenia find that their symptoms intensify during perimenopause, and schizophrenia, most often diagnosed in young adulthood, has a second, smaller peak of onset in women around menopause. Cognitive troubles commonly include having difficulty concentrating, experiencing short-term memory failures, and losing motivation. These can be frustrating or downright frightening. The North American Menopause Society, or NAMS, reports that many perimenopausal women who struggle to think clearly or remember obvious words fear that their symptoms herald not menopause but dementia.

Physical hallmarks such as hot flashes and night sweats don't tell the whole story.

"Women don't know who they are anymore," says Sheryl Spitzer-Resnick, MD '85, a family medicine physician based in Madison, Wisconsin, who specializes in peri- and postmenopausal management.

Several large initiatives, including the landmark Study of Women's Health Across the Nation, or SWAN, the Nurses' Health Study, the Harvard Study of Moods and Cycles, and the Women's Health Initiative, or WHI, have advanced menopause knowledge and care in recent decades. Still, researchers haven't fully characterized the scope of menopausal mental health. Many studies don't include mental health as a primary outcome. Investigators use diverse criteria to measure it. Prevalence estimates for perimenopausal depression alone are as high as 40 percent, says Payne. Stigma, poor access to health care, and other barriers that can impede reporting mental health symptoms don't help.

What is clear is that if approximately 2 million U.S. women begin perimenopause each year, as the MGH Center for Women's Mental Health estimates, then "a large number of women may be at increased risk" for depression and other mood disorders "for an extended time," wrote Hadine Joffe, an HMS professor of psychiatry at Brigham and Women's Hospital and current president of NAMS, and colleagues from the MGH center in *The American Journal of Medicine* in 2005.

Treating mental health as part of an overall menopause management strategy would

JON BLACK

improve individuals' emotional well-being and quality of life and even help prevent stress-related chronic disease—a particularly important effort during this stage of women's lives, says JoAnn Manson, the Michael and Lee Bell Professor of Women's Health at HMS and Brigham and Women's and a former NAMS president.

"This should be a time for clinicians and patients to devote even more attention to risk-factor management, lifestyle modifications, and other approaches to reducing risks of chronic diseases, which rise after menopause," she says.

Addressing mood and cognitive symptoms would also offer social, financial, and communal benefits, given that poor mental health may diminish perimenopausal women's work and relationships. Marriages may grow strained. Personal productivity and confidence may fall.

"Women can't fully contribute to the things they care about," says Spitzer-Resnick, "nor are they as tolerant or resilient in how they manage stress."

"We are losing women's energies in our families, our workforce, and our communities because we have not given parity to mental health," says Haygood.

Alleviating this quiet tragedy requires understanding its origins in and around the body.

Lived experience

Chronic pain from endometriosis and recurrent ovarian cysts drove Spitzer-Resnick to have her uterus and ovaries removed at 39. The aftermath, she says, taught her "hormones by fire."

It's impressive to consider how much havoc two organs weighing a few tenths of an ounce can wreak.

She couldn't sleep past 4 a.m. She snapped at her husband. She "hot flashed [her] brains out." Wearing the maximum allowed dose of estradiol patches finally helped her sleep through the night.

At first, she attributed the remaining anxiety and irritability to her "crazy busy life" running a family medicine and obstetrics practice and raising a child. Then she heard about natural progesterone supplements at a conference, started taking them, and felt calmer. The hot flashes ebbed.

At its essence, menopause is hormones. The ovaries shut down, taking with them the estrogen, progesterone, and testosterone they produce. As ovary activity lessens, the levels of these hormones surge and drop unpredictably. A person's baseline levels seem to matter less than the fluctuations.

It's impressive to consider how much havoc two organs weighing a few tenths of an ounce can wreak. Then again, there are estrogen receptors distributed throughout the body.

Researchers, including Joffe, continue to uncover ways in which reproductive hormones, particularly estrogen, affect the brain. Low estrogen levels in the hypothalamus have been shown to drive hot flashes, night sweats, chills, and insomnia. Concentrations of estrogen receptors in the hippocampus help explain the hormone's involvement in memory and cognition. Studies indicate that estrogen modulates dopamine, serotonin, and norepinephrine activity from the amygdala to the prefrontal cortex, influencing mood stability and offering one explanation for the association with schizophrenia.

Clinicians such as Spitzer-Resnick remind researchers not to discount the potential effects of low progesterone, either: "your happy, anti-anxiety, anti-inflammatory hormone." Having seen natural progesterone supplementation ease her own and an array of her perimenopausal patients' symptoms, including panic attacks and uncontrolled crying, she's eager for scientists to dig deeper into progesterone's role at the root of menopausal mental health. Measuring women's reproductive hormone levels, especially at different times of the month, would provide invaluable data, she and others say.

Hormones can affect perimenopausal mental health indirectly as well. The constellation of possible physical symptoms—thermostat swings, unpredictable periods, weight gain, breast changes, thinning hair, lower libido, discomfort during sex—can leave women anxious and depressed. Sleep disruption tanks mood and clarity of thought. Brain fog may generate worry about professional life.

"If you're a doctor, a university president, a writer, really all women need their words," says Spitzer-Resnick. "Lowering estrogen levels seems to make people forget their nouns."

Yet hormones account for only a piece of the puzzle. Simple lines can't be drawn from most perimenopausal mental health symptoms to changes in biochemistry. Notably, clinical trials have failed to find a direct link between menopause and major depression. Research may unearth additional biological and genetic contributors. Psychosocial factors also appear to play a significant role.

Experts point to life events that tend to coincide with menopause, which U.S. women reach at an average age of 51. Middle-aged women may be dealing with ailing parents, children leaving or returning home, or changes in their domestic relationships. They may shoulder new responsi-

"We are losing women's energies in our families, our workforce, and our communities because we have not given parity to mental health."

bilities at work or confront the first hints of ageism. The passage of time can't be ignored.

"Menopause is the undeniable indicator of aging," says Green. "It brings a lot of existential questions to the fore."

The intersection of menopause and middle age makes it hard to track every symptom to its source. "Hormonal and physiological changes overlap with, and compound, the stressful life circumstances many women experience in midlife," says Manson.

Going through menopause earlier than expected carries its own set of mental health issues. A 2019 article in *Post Reproductive Health* described how patients undergoing induced menopause via procedures that remove or disrupt the ovaries, along with the approximately 1 to 3 percent of women who experience natural menopause before age 40, may experience grief, anger, depression, and anxiety.

Cultural standards of femininity may clash with bodily changes. Workplaces typically don't accommodate the need to adjust temperatures or leave meetings to ride out hot flashes.

And people with ovaries who don't identify as women may need support as they traverse a traditionally female phenomenon.

External pressures to hide or overcome symptoms take an additional toll. Women are often expected to prioritize the needs of others. Cultural standards of femininity may clash with bodily changes. Workplaces typically don't accommodate the need to adjust temperatures or leave meetings to ride out hot flashes, and many women don't feel comfortable raising menopause-related issues at work while they still struggle for equal pay and respect compared to men. Mental health issues continue to carry a stigma of weakness, says Haygood. Too many women who reach out on social media with their struggles over menopause and mental health end up feeling shamed or inadequate, says Green. Silence often wins out—and women lose.

"Menopause and mental health is still a forbidden topic in our society," says Payne. "It's mind-boggling. Every woman will go through menopause, yet how often do we talk about it?"

Unfortunately, the medical profession is not ideally positioned to help.

Ask the question

Stigma certainly prevents some perimenopausal women from telling care providers about mental health struggles. Obstacles arise on the other side, too, starting with the constraints on the time a physician can spend with a patient.

"Any clinician with a schedule to keep will often not ask women about mental and sexual health for fear they'll open a Pandora's box that will make them late for their next patient," says Green. She resists these tendencies in the women's health practice she cofounded in San Francisco.

Sheryl Spitzer-Resnick

Even when women disclose, insurance reimbursement practices, instances of medical sexism, and gaps in physician education can create barriers to effective care. Lobbying for equitable coverage of mental health services and other treatments and for implementation of standard mental health screening in perimenopausal women would make a big difference, say Green, Haygood, and others.

While discrimination has fallen in recent years, the medical profession can do a better job of listening to female patients, sources say. Perimenopausal women of color may be at an even greater disadvantage, considering studies have demonstrated that women of color are routinely treated differently and have a harder time accessing mental health services than white women, says Haygood.

"Some providers take Black women less seriously when they seek remedies for mental health concerns, just as they do with other symptoms," she says.

Awareness of the need to address mental health issues around menopause has outpaced provider training in how to do so. A 2013 survey published in *Menopause* found that only one in five U.S. OB-GYN residents receives formal training in menopause care. Medical school curricula tend to offer "quite limited" information on menopause, Manson says.

HMS faculty are trying to change that. This spring, Manson and colleagues launched an elective course focusing on sex- and gender-informed medicine. Among the topics covered are hormonal, vascular, and mental health changes at various life stages and the best ways to address related health issues.

Follow the science

Most women don't need prescription medications to traverse perimenopause. For those who do, hormone replacement therapy offers a top option—or would, if it weren't for widespread misinterpretation of findings from the WHI in 2002. That study saved lives by revealing that a type of estrogen-progestin therapy raises risk of heart attack, stroke, and breast and endometrial cancers when prescribed to late menopausal and postmenopausal women solely to prevent chronic disease. Inappropriate use of hormone therapy plummeted, but so did other, safer applications.

The WHI report went public on a Wednesday. Green watched in growing alarm on Thursday as news story after news story "took something that was statistically interesting but not overwhelming and turned it into a crisis." Friday morning, as part of her weekly medical segment on KTVU news in the Bay Area, Green went on the air and tried to impress upon her audience the difference between relative and absolute risk. Yes, she explained, breast cancer risk doubled, but that amounted to only one extra case per 12,000 women per year.

Green's voice, along with colleagues', was drowned out. The message got lost that hormone therapy remains a good strategy for managing "moderate to severe" symptoms such as night sweats in perimenopausal women who don't have a high risk of breast cancer or other contraindications—and that steadying the hormonal seesaw can improve mental health. To this day, many doctors do not prescribe FDA-approved hormones, many women have been afraid to take them, and most health plans won't cover many of the safest forms of estrogen replacement.

Manson served as a principal investigator in the WHI and several other women's health studies. She pursued women's health to prevent disease after her mother died of ovarian cancer early in Manson's medical training. Although encouraged by progress in the field, she says it's "been frustrating to see the WHI results extrapolated to women in their forties and early fifties who are grappling with severe and distressing menopausal symptoms."

Communication and education could help. So could more research into formulations that the original WHI report didn't cover, such as estrogen patches and bioidentical hormones. Evidence would then replace conflicting anecdata, such as natural progesterone serving as a magic bullet for Spitzer-Resnick while causing endometrial buildup that necessitated a hysterectomy for Green. More research into the safety of long-term hormone therapy would inform care for cisgender women and for transgender women who take estrogen and anti-androgens and who have the option to continue hormones indefinitely or to taper them for a menopause-like experience. A survey of transgender women in the UK reported in the *International Journal of Transgenderism* in 2018 found that most respondents over 50 had not changed regimens; the hormones provided critical mental health support by helping them look and feel more feminine, boosting self-confidence, and reducing depression.

Research is still in its infancy regarding the menopausal experiences of certain populations, such as transgender men who keep their ovaries.

The other common strategy for tackling perimenopausal women's mental health is to prescribe antidepressants and anxiolytics. One theory holds that these drugs compensate for estrogen's waning effects on serotonin and gabapentin. There's some suggestion that they tamp down hot flashes and night sweats, further improving mood and cognition. A concerning number of studies, however, have found perimenopausal depression and anxiety resistant to these drugs.

While the jury deliberates on whether antidepressants or hormones provide the better first-line pharmacologic treatment, researchers seek more options. Cognitive behavioral therapy helps many perimenopausal women. HMS faculty are investigating a wide range of therapeutics, including neurosteroids and dietary supplements. Studies have begun to probe the roles of inflammation and the gut microbiome. Research is still in its infancy regarding the menopausal experiences of certain populations, such as transgender men who keep their ovaries.

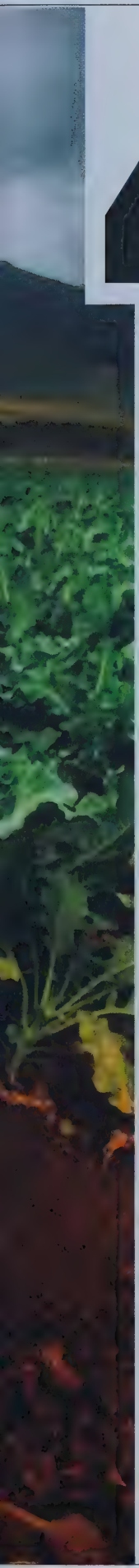
As menopause research and care enter a new phase, so do those who cross the threshold. Postmenopausal health requires just as much attention as—if not more than—health before menopause. With U.S. female life expectancy hovering around 81 years, one third of menopausal women's lives still lie ahead. HM

Stephanie Dutchen is a science writer in the HMS Office of Communications and External Relations.

Pesticide use, changing with the climate, threatens reproductive health

What We Sow

BY STEPHANIE DUTCHEN



"IT IS IRONIC TO THINK THAT MAN may determine his own future by something so seemingly trivial as the choice of his insect spray," wrote Rachel Carson in *Silent Spring*, her groundbreaking 1962 book on the hazards of pesticides.

Nearly sixty years later, experts still struggle to uncover and mitigate the effects of pesticides on human health, including reproductive health.

To date, exposures to certain plant-, fungus-, and insect-killing chemicals have been linked to impaired fertility in women and men, reduced sperm count and quality, miscarriage, premature birth, stillbirth, birth defects, low birth weight, and developmental disorders.

Nine percent of men and 11 percent of women of reproductive age in this country report fertility problems, according to the U.S. Centers for Disease Control and Prevention. The extent to which pesticide exposures contribute to these has not been pinned down. That's partly because we live in a web of genetic and environmental factors that are hard to disentangle.

It's also because the best way to show that a particular pesticide is harmful to human health is to run a randomized, controlled clinical trial, but exposing individuals to pesticides before, during, or after pregnancy would be unethical, says Carmen Messerlian, an assistant professor of environmental reproductive, perinatal, and pediatric epidemiology at the Harvard T.H. Chan School of Public Health. Such work, however, may not be necessary. Messerlian explains that laboratory, animal model, and observational human studies have delivered ample evidence that some pesticides make it harder to bear healthy children.

Farm to table

People are using more agricultural and residential pesticides as the climate changes. Experts anticipate that, as a result, chemicals old and new will increasingly leach into soil and water or become airborne, causing more health problems.

Studies indicate that warmer, wetter areas have more frequent and more severe crop disease outbreaks. Pests enter new regions and survive milder winters in greater numbers. More atmospheric carbon dioxide produces hardier weeds. Droughts parch contaminated land, making it easier to inhale pesticides. Preliminary research is raising concerns that human skin may absorb chemicals more easily in the heat and investigating whether heat-stressed humans process chemicals differently.

Although people who work directly with pesticides are at greatest risk of experiencing reproductive health repercussions, most of the U.S. population is exposed to these chemicals, largely through residues in food and water. Women who are pregnant or planning to have children face particular hazards. A 2018 study in *JAMA Internal Medicine* led by researchers at the Harvard Chan School, for example, found that among women undergoing infertility treatment, those who ate conventional fruits and vegetables had fewer successful conceptions and live births than those who ate organic produce.

Researchers have identified three windows of vulnerability. Before prospective parents conceive, pesticides may compromise eggs and sperm and disrupt hormones that regulate physiological processes such as menstrual cycles and blood sugar levels. During pregnancy, exposures may alter gamete formation and neurological development in the fetus. Researchers, including Tamarra James-Todd, the Mark and Catherine Winkler Assistant Professor of Environmental Reproductive and Perinatal Epidemiology at the Harvard Chan School, have begun exploring pregnancy and its postpartum risks, including maternal metabolic health.

Today and many tomorrows

Much remains to be explored. Which of the thousands of new or approved pesticides used in the United States cause reproductive harm? At what exposure levels? Which chemicals interact to change one another's effects?

To help narrow the suspects, Monica Colaiácovo, a professor of genetics in the Blavatnik Institute at HMS, developed a system that uses *C. elegans* nematodes to quickly screen for whether a chemical affects egg formation, embryonic development, or early worm life. Those that do have these effects can be investigated in animal models and flagged for the U.S. Environmental Protection Agency's reviews of pesticides of concern.

Epidemiologists, meanwhile, should move away from the traditional method of taking thirty years to study individual chemicals and instead start determining how entire classes of pesticides affect reproduction, says Blair Wylie, MD '00, an HMS associate professor of obstetrics, gynecology, and reproductive biology at Beth Israel Deaconess Medical Center.

With insights come opportunities to reduce harm. Messerlian launched a pilot study testing behavioral interventions for couples. She joins others in encouraging prospective parents to reduce pesticide exposure by eating organic foods, while being mindful that many people can't access or afford pesticide-free groceries.

Focusing on personal responsibility not only favors the privileged but risks blaming victims for unwanted reproductive outcomes, warns Wylie. Individuals' options are limited. Many pesticides are inescapable; some, including DDT, persist in the environment for decades.

Top-down solutions therefore must complement those that start at the bottom. Clinicians have power here, too. "We can use our voice to raise concerns at the governmental level," says Wylie. "Public health can move the needle a lot."

Clinicians also can educate themselves and their patients. They can tap resources such as the Pediatric Environmental Health Specialty Units, a network for which Wylie serves as a reproductive health specialist.

With socioeconomic disparities in pesticide exposures documented, clinicians and researchers can try to improve reproductive health equity through environmental justice-based work and community engagement, says James-Todd.

The challenges are many, but so are the opportunities. "There's so much we can all learn and try to improve," says Colaiácovo, and with climate change breathing down humanity's neck, "we don't have a lot of time." HM

Stephanie Dutchen is a science writer in the HMS Office of Communications and External Relations.

Women are advocating

for advances in women's health

IN 1970, A TYPEWRITTEN 193-PAGE BOOK, *Women and Their Bodies*, by the Boston Women's Health Collective, shocked and changed the nation. In an era when doctors, nearly 93 percent of whom were male, patted women on the head and told them not to trouble themselves with what was in the pills they were taking, routinely dismissed their symptoms as psychosomatic, and spoke to their husbands as if the patient herself wasn't in the room, the book covered, openly and in detail, such taboo topics as menstruation, birth control, and abortion. Religious leaders labeled the book obscene, and it was banned from high schools and public libraries.

Now a classic in its ninth U.S. edition, the book, which in 1971 became *Our Bodies, Ourselves*, was revolutionary: It introduced a wide audience to the concept of women taking charge of their own health. Since its release, women's health has come a long way, not only in public awareness but also in the changing face of the medical profession and the recognition that from a research perspective, "we can't just assume women are little men," according to Dara Kim Lee Lewis, MD '92, an HMS instructor in medicine and associate physician at Brigham and Women's Hospital and co-director of the Women's Cardiology Program and director of noninvasive testing at the Lown Cardiology Group in Chestnut Hill.

But women still have far to go before they reach parity with men in all aspects of health care.

"There are a lot of different parts of the medical ecosystem with many different players, and each one needs a different intervention," says Anula Jayasuriya, MD '89 PhD '91, who in 2013 founded the venture fund EXXclaim Capital, which was a pioneer in its focus on investing in women's health.

For women, she says, it's vital to have an increased awareness of the gaps in women's health research and advocacy to remedy the status quo. For physicians and other health care providers, it's essential to understand biological differences between sexes and genders in order to deliver optimal care. For academics, it is crucial to get women into trials and to analyze the sexes separately in order to generate accurate scientific outcomes, and governments need to incentivize that goal. Entrepreneurs, Jayasuriya says, need to consider the unmet needs of women when exploring novel devices, diagnostics, and therapies, and investors need to fund them. Then, she adds, "the company developing the innovation has to go through a whole chain that ultimately results in success when some bigger company buys it or it goes public and provides good financial returns to investors who took the risk and funded it."

A Place in the Room

BY ELIZABETH GEHRMAN

JORI BOLTON

Anula Jayasuriya

JAY WATSON

Underlying it all is a basic truth that's often overlooked. "Understanding women's health helps men's medicine too," says Eliza Lo Chin, MD '93, executive director of the American Medical Women's Association (AMWA) and an assistant clinical professor of medicine (voluntary) at the University of California San Francisco. "That's why AMWA calls it sex and gender health rather than women's health," Chin says. "Because it's about improving health care for everyone." By analyzing the sexes separately, for example, researchers have discovered that colon cancer tends to strike men earlier in life than it does women, that depression is more common in women but deadlier in men, and that men are more likely than women to develop Alzheimer's at a younger age.

To start making headway in discerning sex- and gender-related differences in health outcomes, says Chin, we must first recognize that "women's health isn't just what some people would term 'bikini medicine', that is, with the focus on breast and reproductive health. We still focus on traditional women's issues like cervical cancer, which is on the horizon for eradication, but it's also about all these other systems."

"One way to parse the universe," Jayasuriya suggests, "is 'only in women', which would be reproductive health; 'predominantly in women'—some examples are autoimmune diseases like lupus and rheumatoid arthritis—and 'different in women', like cardiac disease, which is furthest along in our understanding."

We now know, for example, that heart disease, the leading cause of death in the United States, can present differently across sexes, with women more likely to have symptoms such as extreme fatigue, indigestion, and neck or shoulder pain rather than chest pain. Yet despite several massive public health campaigns over the past two decades, women still have a 50 percent greater chance of getting an incorrect diagnosis, even after having had a heart attack. According to a 2020 study in *Circulation*, only 38 percent of participants in cardiac trials are women. However, women can have worse outcomes from certain types of heart attacks. According to 2018 research from Sweden's Karolinska Institute and the UK's University of Leeds, women with acute

myocardial infarction had higher excess mortality than men. This finding, says the World Heart Federation, indicates that women are "up to three times more likely to die following a serious heart attack than men as a result of receiving unequal care and treatment."

Listen to the women

If our understanding of how the highest profile, biggest-killer disease affects women still hasn't reached parity, what hope do we have? Most experts say achieving balance starts with research. Historically, women were left out of scientific studies because, well, they were women; then, in more recent times, according to gender historians and other scholars, the variability introduced by hormones was blamed. In 1977, the FDA issued guidance recommending that women of childbearing age be excluded from the early phases of drug evaluation studies, largely in response to the thousands of stillbirths and birth defects caused by the use of the drug thalidomide in pregnant women with nausea in the late 1950s and early '60s.

Historically, women were left out of scientific studies because, well, they were women.


Marsha Henderson

MARK FINKENSTAEDT

But as the years passed and feminism became more the norm, women grew increasingly vocal about the absurdity of medical science basically ignoring half the population, and by 1987 the National Institutes of Health urged the inclusion of women in its guide for grants and contracts. When the General Accounting Office later found poor adherence to this recommendation, Congress passed the NIH Revitalization Act of 1993, which, among other things, required grantees to include women and minorities in their cohorts.

Today, while many research groups are made up of men and women in equal proportions, many still are not, depending on the field of medicine, the trial phase, and other factors, according to a study published in *JAMA Network Open* in 2019. The possibility of women being unknowingly pregnant while in a trial remains a fear for many researchers, but usually by the time human trials begin, says Siobhan Dolan, MD '93, vice chair for research in the Department of Obstetrics, Gynecology and Reproductive Science at Mount Sinai Health System in New York City, "animal and theoretical data are pretty clear that there is or isn't a risk to pregnancy. I'm not saying pregnant women should be first in line for studies, but when pregnant people are systematically excluded from all studies, are we hurting women in the name of helping them?" The very idea that pregnant women need special protection, she suggests, is paternalistic. "Women can make decisions," she says. "They're super smart. Give them the data, obtain informed consent, and respect their autonomy."

Technology may soon be used to get around this issue in some cases. Three-dimensional organ-on-a-chip systems, which attempt to simulate the mechanisms and responses of entire organs, can be used to mimic the menstrual cycle, the female reproductive tract, and the placenta and to test whether drugs taken during pregnancy can cross the placenta to the fetus.

It isn't only women who are underrepresented in research and clinical trials, though. "Even when there is an equal number of women, the question is who are the women?" says Marsha Henderson, a retired associate commissioner for women's health at the U.S. Food and Drug Administration. "There's a dearth of people of color in these trials, and it's a problem."

The coronavirus pandemic showed that this needn't be the case. "Vaccination companies planned in advance and they had good diversity," she says. "They had to, because their market for the vaccine was worldwide."

Older people, too, are underrepresented in studies overall and even in those for the COVID-19 vaccine, according to a study published in *JAMA Internal Medicine* in September 2020, although the disease has had

"Even when there is an equal number of women, the question is who are the women? There's a dearth of people of color in these trials, and it's a problem."

a disproportionate effect on them. Even male research mice outnumber female ones by as much as five to one, and bench scientists rarely consider whether the cell lines they're using are male- or female-derived, though a 2014 study found that "far from being irrelevant, genes expressed on the sex chromosomes can have a marked impact on the biology of such diverse tissues as neurons and renal cells."

The seats of power

And it's not only research cohorts and materials that are unequal; it's who is doing the studies. "We have to look at subsets of misogyny," says Suzanne Poppema, MD '74, author of *Why I Am an Abortion Doctor* and a founder of Physicians for Reproductive Choice and Health in New York. "There are a lot more women and people of color going into medicine now, but they're still not getting leadership positions."

In 2019, for the first time, women slightly outnumbered men in medical schools, though UNESCO has found that worldwide, less than a third of researchers are female. Fewer women are principal investigators, and among first-time PI grant recipients, women received a median of nearly $127,000 in funding compared with a median of almost $167,000 for men, according to a 2019 study from Northwestern University.

The disparity was even worse at the university level. As more women start practicing, the focus of research should start to shift, says Lee Lewis, because "there's a special thing that happens when a lot of women become doctors. It's that people start paying attention to things they never have before. If you haven't experienced it, it's hard to really understand PMS, menopause, pregnancy, and menstrual cramps."

But still, "you can't assume a female doctor who's been through the same medical education and read the same studies as a man will be better at recognizing issues just because she's a woman," says Elizabeth Garner, MD '94. Garner, an OB-GYN and chief medical officer at ObsEva, a clinical-stage biopharmaceutical company specializing in women's reproductive health, knows from firsthand experience just how insidious it can be to not be able to identify with your patients. "My listening skills and the way I interacted with my patients, especially those in the postpartum period, changed completely once I had a baby. Completely, overnight."

Among first-time PI grant recipients, women received a median of nearly $127,000 compared with a median of almost $167,000 for men.

Elizabeth Garner

ANDREW PICCONE

Many agree that change needs to focus on those who hold the purse strings the vast majority of the time. "It's not that men aren't interested," says Garner. "They're just not aware. Of the hundreds of investors I've met with, I'm going to guess maybe fifteen to twenty-five have been women. And when a woman is in the room, she's generally not the decision-maker; after her meeting with us she presents our story to whomever actually makes the call, and that's virtually always a man." Yet even though women might rarely be in the room—the National Venture Capital Association puts the percentage of male partners in venture capitalism at almost 90—once men are exposed to the actual numbers, Garner says, "they're like, 'Wait, what? Contraception is a $5 billion market?'"

"I don't understand the disconnect," she adds. "Not only is half of the world's population female, but women make most of the health decisions for their families."

To date, women's health has been perceived as less lucrative, says Jayasuriya, with many investors and pharmaceutical companies considering it a niche market. "Many women are aghast at this view," she adds. "Their rejoinder is to ask how it can be a niche when women make up more than fifty percent of the population." But numbers, she points out, are only one metric. It's also about the price the market will bear.

"Look at the 'hot' pharmaceutical sectors today," says Jayasuriya. "The focus is on markets that are small, based on the numbers: immuno-oncology, rare or orphan diseases, gene and cell therapies. Why? Because the pharmaceutical model today is not about the size of the market; it's about what you can charge. If you can charge half a million or even a million dollars per patient to a few people rather than fifty dollars to millions of people, it's more efficient: You can employ a much smaller sales force."

Perhaps, but according to the 2019 book *Vagina: A Re-education*, by the London-based journalist Lynn Enright, erectile dysfunction, which affects about a fifth of men, is studied five times as much as premenstrual syndrome, which the MGH Center for Women's Mental Health says affects up to 90 percent of women with regular menstrual cycles.

The tech advantage?

That kind of imbalance is finally beginning to change, in part thanks to technology. Tele-

medicine, for example, which holds great promise but has been bogged down by regulatory and insurance issues, became common during the pandemic. It's expected to continue as part of the health care landscape once things return to normal, allowing people in underserved areas, overscheduled women dealing with childcare and transportation issues, and rural residents to have greater access to doctors and mental health providers. "The biggest obstacle to telemed has been acceptance, by the patient and the provider," says Henderson. "That has gone away. We have it now and don't want to lose it."

Telemedicine is also providing a somewhat under-the-radar solution to one of the biggest ongoing problems for women's health in this country: abortion access. Poppema works with a service that provides internet-based medical supervision for women all over the country to quickly get mifepristone and misoprostol, popularly known as the abortion pills.

"When clinics here were allowed to reopen after the initial COVID-related closings, they realized they could do no-touch abortions by telemed," Poppema says. "Medical abortions have a long track record of safety; they're totally private because no one can tell you took the medications; and they give women back their most basic human right: personal autonomy."

Beyond that huge step, which is being challenged by many conservatives in Congress and is expected to be heavily litigated, the financial data and software company Pitchbook predicts that "femtech," or software and tech-based devices, diagnostics, products, and services focused on women's health, will be a $3 billion industry by the end of this decade.

"The advent of digital health brought down the barriers to entry for entrepreneurs," says Jayasuriya, "so there's been a burgeoning of opportunities in apps and wearables." They may not make doctors or society take women more seriously on issues like period pain or menopause, she says, "but they empower women to take their own health more seriously, which may eventually help move the needle."

While the apps are selling better than expected and there's a fair amount of media buzz out there about femtech, Jayasuriya says, "what lags is how much money there is to be made. There haven't been that many big successes yet. So although the pipeline is expanding, the exit part of the ecosystem—IPOs and acquisitions—is lagging. The business case has to be compelling."

Forbes recently called women's health care "a market ripe for disruption," and there's some indication that that's beginning to happen. "When it comes to women's health, people often say the big pharma companies have 'left the building,'" says Garner. "They just don't want to do it. It's a lot of work to explain future potential in women's health to investors, especially given the current focus on cancer and rare diseases. But what's promising is that now that seems to be changing."

The movement among investors may be getting a boost from greater awareness and women's willingness to be more vocal about their concerns.

Merck just spun off its women's health division into a new company called Organon, which, according to the investor site The Fly, is expected to generate more than $6 billion in revenue this year and aims to be a leader in the field. Health care giant Bayer expanded its women's health care drug development pipeline in 2020 by acquiring a UK-based biotech company that is working on a novel treatment for hot flashes—one that is based not on replacing hormones but on short-circuiting the signaling pathway. "Giving or blocking hormones is very effective for many conditions that affect women," says Garner, "but there are associated risks, and the research sort of ends there. So, it's very exciting to see efforts to better understand the root cause."

The movement among investors may be getting a boost from greater awareness and women's willingness to be more vocal about their concerns—perhaps, say Lee Lewis and Garner, thanks in part to the Me Too movement's breaching the dam of silence. We still haven't completely overcome the stigma of discussing women's health that prevailed when *Our Bodies, Ourselves* came out, they say, but doing so can only lead to better outcomes. "Infertility, miscarriage, hot flashes, heavy bleeding," says Garner, "these are challenges that so many women face, yet most of us suffer in silence. A woman might take a day off from work because she's having a particularly heavy period and won't tell her boss why, even if that boss is a woman. If we can't even share this stuff with other women, how the heck are we going to increase the visibility of all the health issues we're dealing with on a daily basis?"

Still, says Lee Lewis, women's health is finally getting on people's radar. "Doctors and patients are starting to recognize that we have different biology, different genetics, and different risk and experience, and require a different approach," she says, "and it has shined a light on this problem. It hasn't happened overnight, and we'll continue to advance over many more decades, but the light is on, and that's a reason to be optimistic." HM

Elizabeth Gehrman is a Boston-based writer.

"Not only is half of the world's population female, but women make most of the health decisions for their families."


Estrone
Estriol
Console
Accessory Tray
Key/Clip
Motor Hood

Good

The field of exercise oncology is bringing benefits, hope to survivors of breast cancer

BY JESSICA CERRETANI

Moves

THE OARS SLICE IN AND OUT of the water in unison as the boat glides downstream. To an observer, it looks like any other group of rowers enjoying a sunny day on the Charles River. But this all-female team of athletes has more than their love of rowing in common: They are all breast cancer survivors, bound together by their desire to stay strong and active.

These women, and their peers in boats across the country, have long understood through lived experience that regular exercise has powerful effects on both the bodies and minds of people with cancer. Today, science is finally catching up with them.

Just a few decades ago, advice to cancer patients, particularly those undergoing chemotherapy, centered on rest: Take it easy. Avoid strenuous activity, especially aerobic exercise. At the time, the recommendation seemed logical. Allowing the body to rest might also allow it to heal, experts thought, while physical activity might worsen fatigue, pain, and other symptoms.

This thinking began to change in the late 1980s, when a pair of oncology nurses at The Ohio State University undertook what was then a radical experiment. Curious to see whether conventional wisdom on exercise avoidance held true, they randomly sorted forty-five breast cancer patients who were undergoing chemotherapy into a group that participated in ten weeks of aerobic exercise training or into a control group. The findings of this landmark study were stunning: Not only was exercise safe and feasible during cancer treatment, it was also associated with improvements in weight, body composition, and nausea symptoms. The small trial served as a catalyst for future investigations, ultimately leading to a new field of study: exercise oncology.

In 2010, researchers and clinicians gathered at an interdisciplinary meeting to review the evidence on the safety of exercise in people living with cancer. The resulting American College of Sports Medicine (ACSM) Roundtable report—one of the first of its kind—advised cancer survivors to avoid inactivity.

Eight years later, the roundtable met again to assess the data; that assessment led the group to expand its recommendations to include the role of exercise in cancer prevention, control, and survivorship. The guidelines offer a powerful prescription for people with cancer. The evidence to support these guidelines is overwhelmingly reassuring: Studies suggest that regular physical activity is associated with fewer or milder side effects from chemotherapy, improved quality of life, and even lower odds of cancer recurrence and mortality. While research continues, leading investigators in the field say that every physician and other health

DUNG HOANG

care provider should consider prescribing exercise to their patients with cancer.

"We're at the point where we know exercise is an evidence-based treatment with robust effects," says Kathryn Schmitz, a researcher at the Penn State Cancer Institute who chaired the ACSM's roundtables. "If we don't prescribe it, when does that become malpractice?"

Weighty issues

Since exercise oncology's infancy, much of the research in the field has focused on breast cancer. That's largely because of the prevalence of the disease, which, according to a 2020 NIH report, is the most common type of cancer among women in the United States. It also affects about 1 percent of men and can occur in transgender and nonbinary people assigned female at birth.

As with some other cancers, overweight or obesity can heighten the risk for breast cancer in postmenopausal women. Indeed, one recent meta-analysis of eighty-two studies found that the risk of dying from breast cancer was 35 percent higher among women who were obese at the time of their diagnosis, compared to the mortality risk for women who were within standard weight ranges.

Although researchers are still unraveling the relationship between weight and breast cancer, hormones appear to be an important link. In postmenopausal women, fat cells play an important role in the production of estrogen, which can spur tumor growth in hormone receptor-positive breast cancers, says Elizabeth (Betsy) O'Donnell, an HMS

In postmenopausal women, fat cells play an important role in the production of estrogen, which can spur tumor growth in hormone receptor-positive breast cancers.

assistant professor of medicine at Massachusetts General Hospital and director of the hospital's Lifestyle Medicine Clinic. Body fat can also trigger chronic low-grade inflammation, a state shown to stimulate the growth of breast cancer cells in postmenopausal women.

These factors "uniquely position" exercise as an "intervention to manage body weight for risk reduction and improved outcomes in women with breast cancer," says Christina Dieli-Conwright, an HMS faculty of medicine member who studies the effect of personalized exercise interventions on cancer outcomes at Dana-Farber Cancer Institute. Most of the seminal research in this area has involved breast cancer, she says, "in part because of the volume of patients we can recruit."

From the 1990s to the mid-2000s, the majority of research examined the effects of physical activity on the quality of life in women living with breast cancer, particularly those undergoing treatment for the disease. The 2010 ACSM roundtable, which drew mainly from studies of people with breast or prostate cancer, determined that exercise training was generally safe and well-tolerated both during and after cancer treatment. Beyond safety, the panel found sufficient evidence to conclude that exercise could elicit improvements in physical fitness, physical functioning, and quality of life and decrease fatigue in patients with cancer.

By 2018, the data on these topics were sufficient to allow the ACSM roundtable to develop evidence-based prescriptions for the frequency, intensity, time, and type (FITT) of exercise best suited to specific cancer-related health outcomes. The panelists, in fact, found strong or moderate evidence to issue FITT prescriptions for eight such outcomes: anxiety, depressive symptoms, fatigue, quality of life, lymphedema, physical function, bone health, and sleep. Most of the FITT prescriptions entail moderate aerobic activity, often combined with resistance training, several times a week. Similarly, the American Cancer Society recommends that people with cancer remain as active as possible during treatment and aim for at least 150 minutes of activity a week once their disease is stable or in remission.

The panel concluded that regular exercise both before and after diagnosis might improve survival in people with breast or colon cancer.

"The evidence we have clearly suggests that exercise can help mitigate the toxicities of cancer treatment," explains Jennifer Ligibel, an HMS associate professor of medicine at Dana-Farber and director of the cancer institute's Leonard P. Zakim Center for Integrative Therapies and Healthy Living. "Our message should be that exercise is a goal for all cancer survivors."

The promise of such benefits is what draws many patients to the Zakim Center and the Lifestyle Medicine Clinic at Mass General. Both practices offer exercise and nutritional consultations, as well as other complementary approaches aimed at helping to improve quality of life and attenuating treatment side effects in people with cancer. At O'Donnell's clinic, women with breast cancer make up roughly 90 percent of referrals. Many of the women are driven by a desire to shed pounds following their diagnosis, but more than that, they want a sense of control. "These patients want to know what they can do on their own to feel better," Ligibel says. "Our goal is to help them live the best life that they can after cancer diagnosis."

Define the promise

Exercise may help address the side effects of breast cancer treatment, but could it also help prevent the disease? Could it even stop it in its tracks? These are some of the intriguing questions that some researchers now hope to answer.

"Overall, the field is moving to dig deeper into the effect on clinical outcomes," says Dieli-Conwright. "Now that we know exercise can successfully address quality of life during cancer treatment, we're looking to see whether it can also improve treatment efficacy."

The evidence to date is promising. Engaging in moderate-intensity aerobic exercise for at least 150 to 300 minutes a week and adding in resistance training twice a week appears to lower the risk of mortality from breast, colorectal, and prostate cancers by up to 50 percent. The 2018 ACSM roundtable also confirmed the role of physical activity in helping to prevent several types of cancer, including breast, colon, endometrial, kidney, bladder, esophageal, and stomach. The same panel concluded that regular exercise both before and after diagnosis might improve survival in people with breast or colon cancer. Interestingly, data hint that physical activity following diagnosis may provide greater mortality benefits than exercise before diagnosis.

"These patients want to know what they can do on their own to feel better. Our goal is to help them live the best life that they can after cancer diagnosis."


Kathryn Schmitz

This suggests that cancer patients might have a window of time during which exercise training could influence the course of their disease, says Ligibel. In a 2019 study that appeared in *Clinical Cancer Research*, she and her colleagues conducted a randomized study that looked at the effects of an exercise intervention beginning about a month before surgery in twenty-seven sedentary women with newly diagnosed breast cancer compared with another twenty-two sedentary women with newly diagnosed breast cancer in a control group. They found that, although exercise training didn't appear to influence cancer cell proliferation, women randomized to exercise experienced changes in gene expression in the tumors they had and women randomized to the control group did not. This, says Ligibel, suggests that exercise may have a direct effect on breast cancer—even when started after diagnosis.

Investigators acknowledge that physical activity is useful only if people engage in it.

Ongoing research by Ligibel and others promises to shed even more light on the topic. Her largest undertaking—the Breast Cancer Weight Loss study, known as the BWEL study—will evaluate the effect of weight loss after diagnosis on risk of breast cancer recurrence. The phase 3 study, which enrolled some 3,200 women diagnosed with stage II or III hormone receptor-positive or triple-negative breast cancer, has randomized participants to a health education program either alone or combined with a two-year diet and exercise program. "Our hope is that we'll learn whether weight loss can reduce the risk of cancer recurrence and improve survival in women with breast cancer," she says.

More research is needed to determine exactly how weight loss and exercise might influence cancer prevention and survival. Clues point to certain pathways in tumor growth, including insulin and insulin-like growth factor 1, high levels of which are associated with an increased risk of several cancers. Work by Ligibel, Dana-Farber medical oncologist and HMS Professor of Medicine Jeffrey Meyerhardt, and others has looked at the effect of exercise, the insulin-sensitizing drug metformin, or both on outcomes in breast and colorectal cancer survivors. So far, their findings suggest that the combination of exercise and metformin appears to reduce levels of metabolic markers and inflammation associated with cancer recurrence and mortality.

Just do it

Yet even as they look to the future of exercise oncology, investigators acknowledge that physical activity is useful only if people engage in it. "No matter how sexy the science is, we just need people to move," says Dieli-Conwright.

That can be particularly challenging for breast cancer patients, some of whom may never have exercised regularly before. Others may have been active previously but have fallen out of their exercise routines during cancer treatment. O'Donnell, herself a cyclist, understands that most women aren't likely to adopt her habit of cycling nearly 40 miles round trip to work every day. Instead, she and her colleagues focus on giving cancer patients a boost and breaking down barriers to exercise.

"It can be hard to maintain physical activity if it isn't built into your life," she explains. "And if you've never exercised, you don't know what's out there that you might like." To help, she works with patients to identify forms of exercise that interest them—perhaps a patient hates running but loves to dance, for example—and then create new routines that make activity a habit. She's also created a series of videos to introduce patients to exercise, which she provides free of charge to help acknowledge the financial toxicity of a cancer diagnosis.

But half the battle may be encouraging physicians to prescribe exercise to patients in the first place, says Schmitz. "Medical oncologists tell me that they know exercise is beneficial but don't refer for exercise because they don't have time to discern which patients can safely do it," she says.

In 2019, Schmitz and her colleagues issued a call to action for medical oncologists, urging them to assess the physical activity of their patients, advise patients on

"We're at a wonderful moment in the field of exercise oncology where we have enough evidence to prescribe exercise."

AMANDA BERG KELLY DAVIDSON (PAINTING)

Elizabeth O'Donnell

Findings suggest that the combination of exercise and metformin appear to reduce levels of metabolic markers and inflammation associated with cancer recurrence and mortality.

desired levels of physical activity, and refer patients to appropriate exercise programs. "Preserving activity and functional ability is integral to cancer care, and oncology clinicians are key to providing these referrals," they wrote in the October 2019 issue of *CA: A Cancer Journal for Clinicians*. Indeed, one recent study found that referrals by medical oncologists for exercise training increased from 20 percent to 70 percent when a cancer exercise specialist was embedded in the hospital's chemotherapy suite. The experiment also proved cost-effective, with the price of screening averaging just one dollar per patient.

According to Schmitz, the key to success may require drawing on existing resources. "Referring for exercise can't just be another damn thing for medical oncologists to do," she says. "They already have enough on their plates."

Rather than building new infrastructure, she recommends seeking inspiration from existing clinical pathways. Case in point: psychosocial distress screening, used by medical oncologists to identify anxiety, depression, and other symptoms of cancer-related distress. A similar clinical care pathway could be created to help medical oncologists identify which patients can safely engage in exercise, says Schmitz.

Jumping off point

Looking to the future, investigators hope to further home in on the specifics of prescribing exercise for breast and other cancers. Areas of study include learning more about the benefits of exercise in its many forms, as well as parsing its effects on the many subtypes of breast cancer and determining the ideal "dose" of physical activity for individual patients.

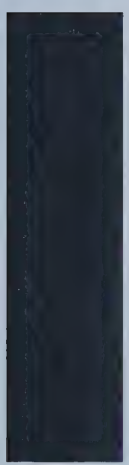
"We're at a really wonderful moment in the field of exercise oncology where we have enough evidence to prescribe exercise, but we still have so much more to learn," says Schmitz. "The fact that we've had some successes doesn't mean we're done—far from it. There's a whole career's worth of investigation left to do in this field." HM

Jessica Cerretani is a Boston-based writer.

Cri de Coeur

BY ELIZABETH GARNER

Funerary Portrait of a Woman
Egypt, Roman Empire, Antonine
Encaustic on linen



AM A WOMEN'S HEALTH PHYSICIAN and I have a mission: I am dedicated to improving the lives of women by caring for them and by educating them about their health and well-being so they may discover a path to a better life for themselves and their families.

I trained in obstetrics and gynecology and gynecologic oncology at the most prestigious institutions in the world and have cared for women with life-threatening malignancies. I have worked on the development of the HPV vaccines known as Gardasil and Gardasil 9. I have helped launch a new test for hereditary cancers, and I have taken a new low-dose contraceptive patch through clinical trials to FDA approval.

I spend every day working on new treatments for serious conditions that deeply affect women and their families. Many would say I have made great contributions to women's health.

Yet every day I wake up to the fact that so much more needs to be done.

Sister power

I am the daughter of a white American mother and a Black Nigerian father. My mother joined the Peace Corps in 1962 and shortly after arriving in Lagos, she met my father, a brilliant young electrical engineer. My parents married in 1964, and three years later moved to Enugu, a town in eastern Nigeria. Eleven days after I was born, the Biafran war started and we fled to Nanka, my dad's rural village. Ultimately, my mother, my older brother, and I were flown out of the country as war refugees. We lived in Cincinnati until the war ended in 1970 and then returned to Nigeria to be reunited with my dad.

My parents worked to ensure we understood and appreciated Nigerian culture. As I matured, though, I observed parts of it that were disturbing. Women and men were not treated equally, and the burden of raising children, cooking, cleaning, fetching water, selling goods at the market, and tending livestock fell to women and their daughters.

But it was also in the village that I learned about the power of women united by a cause. In Nanka, women who are daughters in the same extended family are members of the Umuada, a highly organized group that is central to daily life. Women go to the Umuada with marital grievances, complaints about mistreatment by men, and other domestic and community-related issues. One woman alone is powerless, but when surrounded by her trusted sisters, even the quietest of women will demand justice from an abusive husband or an overbearing brother.

Problem without borders

I came to the United States for college, attended HMS, and trained at Harvard-affiliated hospitals. Early in my career, I became frustrated with the state of women's health, specifically the lack of understanding of and the few effective preventive measures for serious common conditions such as preeclampsia and preterm birth. Furthermore, treatments for several conditions were not based on controlled studies but on anecdotal evidence. It was clear to me that more research was needed to enable targeted prevention and effective treatment of obstetric and gynecologic diseases.

Coming from Nigeria, I was already aware of global inequities in access to health care, but I was shocked by what I witnessed in the United States. The stark differences between the mostly Black or Hispanic, often uninsured or underinsured, women from the neighborhoods surrounding the Boston hospital I worked in and the mostly white, privately insured women from the wealthy Boston suburbs were undeniable. I was reminded of the differences between rich and poor Nigerians that I had always found so troubling.

Just as concerning were the myths and stigma that misinformed my patients and limited their ability to share their struggles with friends, partners, and even me. Worse yet was that health care providers believed some of the myths and reinforced the stigmatization, which led to women's concerns of not being taken seriously, often not being heard at all.

I have seen firsthand the serious and sometimes deadly consequences of stigma, myth, and lack of access. I've treated women living with stigmatized symptoms like heavy vaginal bleeding, abdominal enlargement, vulvar growths, and abnormal vaginal discharge. One of my most memorable patients was an uninsured Vietnamese woman in her 50s who had not left her house in more than a decade because of her steadily increasing abdominal girth. By the time she was admitted to the hospital, her abdomen was the size of a full-term triplet pregnancy; 35 pounds of her 110-pound body weight was her fibroid uterus. Surgery changed her life overnight, but her pain when reflecting on the lost years was palpable.

Compelled to help

Stigma, myth, and lack of access to basic interventions have also touched women in my family. Close relatives have suffered alone and died because of prolonged silence and inadequate resources. These are the stories that truly drive my mission.

The one that has had the greatest effect on me was the death in 2001 of my cousin Georgina, who was a few years older than me and the only female in her family. Georgina was terribly shy and had never married, which I think contributed to her death. With-

out a husband who might have noticed her bleeding during sex, and facing the stigma of sharing such a private matter with her brothers, she quietly bled, possibly for months. Further complicating her situation was that as an unmarried woman with a very limited village education, she could not possibly have had the resources to seek medical help on her own. By the time she presented for care, an ultrasound showed multiple uterine masses; she died shortly thereafter. As her brother Isaac explained to me, "for lack of financial power, [she] developed a complication she could not survive." I was devastated knowing I could possibly have saved her life had I known she was sick.

A call for solutions

In the fourteen years since I left clinical practice there have been major breakthroughs in biomedicine and disease treatment. Yet some of our most prevalent and serious problems remain unaddressed.

For example, we still lack an understanding of the mechanisms leading to preeclampsia, a major cause of perinatal death worldwide. No effective treatment for the disorder exists, other than delivery of the baby. Even after the delivery, mothers remain at risk for complications and death. The United States is the only high-income country where maternal mortality is on the rise, with Black women two to three times more likely to die from pregnancy-related causes than white women.

A 2019 study that appeared in *Morbidity and Mortality Weekly Report* revealed that a large percentage of maternal deaths could be prevented by addressing factors such as access to health care, missed or delayed diagnoses, and the lack of knowledge among patients and providers around warning signs. There remains a void in data on the use of medications such as antidepressants during pregnancy and limited available data on COVID-19 vaccinations in pregnant women.

For many women with recurrent miscarriage or infertility, there are still no identifiable causes. Although significant progress has been made with in vitro fertilization, success rates still hover between 40 and 50 percent and are lower among women of color compared to white women. Menopausal women still lack effective and well-studied nonhormonal therapies for their hot flashes and other symptoms, and in this country each year, about 600,000 hysterectomies are performed, indicating the need for more medical treatments.

And one of the most harmful and persistent myths is that Black women are impervious to pain.

Mistaken thinking

Myth and stigma persist. Although early pregnancy loss occurs in about 10 percent of clinically diagnosed pregnancies, women rarely share their miscarriage experiences, even with friends and family. It is common for women not to tell anyone about a pregnancy until the second trimester for fear of having to admit to a miscarriage. Up to 20 percent of women suffer from mood or anxiety disorders during pregnancy and postpartum. Despite these statistics, postpartum depression and suicidality are still stigmatized.

Rates of infertility are rising, yet this too is often a silent and isolating struggle.

While the mental and emotional consequences of stigma, including stress, anxiety, and depression, have been recognized for decades, mounting evidence suggests a direct link between the elevated cortisol levels and inflammation associated with these illnesses and the risk of conditions including hypertension, diabetes, lupus, preterm labor, and preeclampsia, syndromes that themselves can lead to the same psychological problems that precipitated them.

And one of the most harmful and persistent myths, believed even by some health care providers, is that Black women are impervious to pain.

Progress by inches

Is there any hope here? Well, I do see signs of progress. For one, governmental institutions are recognizing the need for change. In 2018, the National Institutes of Health convened a workshop on predicting, preventing, and treating preeclampsia. In 2019, the U.S. Centers for Disease Control and Prevention awarded more than $45 million for the collection of maternal death data to inform prevention strategies, and, in 2020, released the first data on maternal mortality in more than a decade. In collaboration with Merck, the CDC also has launched the "Hear Her" campaign designed to help women recognize the warning signs of potential maternal health complications and to remind physicians to listen when women express concerns. The Office on Women's Health in the U.S. Department of Health and Human Services continues to advocate for research. Academic institutions and medical associations are also paying increased attention. The Apple Women's Health Study is conducting research aimed at helping to destigmatize menstruation. The Society of Endometriosis and Uterine Disorders' 2021 meeting will focus on dispelling myths and reducing stigma surrounding these conditions, and the American Medical Women's Association has increased its work to advance health equity for women.

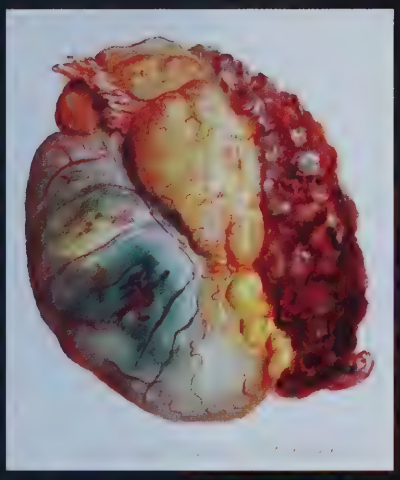
Individual women are also speaking their mind. I've recently read powerful articles on the importance of talking about miscarriage and the "ugly side" that stems from avoiding the topic. Women are blogging about infertility, and last year, the actress Viola Davis made headlines when she openly described her menopause journey as "a dark hole."

These developments are encouraging. Now we must keep the momentum going by calling on women throughout health care to work toward meaningful advances. Having more women at the helm of governments, investment firms, companies, boards, and academic medical centers is also critical to catalyzing change.

Landscape-changing actions, however, will happen only when the united voices of women become so deafening they can no longer be ignored. This is where we can learn from my Umuada sisters. By standing together and encouraging one another to talk freely about our infertility, our miscarriages, our suffering, and our sorrow, we will ultimately eliminate the myths and stigma that prevent women from demanding more investment in research, prevention, innovative treatments, and access. Together, I believe we can and will succeed in driving our health care agenda and making our dreams of a better life for all women a reality. HM

Elizabeth Garner, MD '94, is vice president and chief medical officer for ObsEva, a women's health company based in Geneva, Switzerland.

Art for medicine's sake defined the HMS career of an unsung illustrator



Watercolors of an ovarian fibroma (top) and a testicular sarcoma showcase Byrnes' artistic style and keen eye for detail.

USING FINE LINE and striking color, Florence Byrnes turned surgically removed tumors, diseased appendices, and ulcerated feet into enduring works of scientific art. Byrnes was born in Boston in 1875. Unlike those of the HMS faculty members with whom she collaborated, her story isn't noted in the School's histories. But her skill is well-preserved in the watercolors and drawings in the Warren Anatomical Museum. As early as 1898, Byrnes was working in HMS' surgical laboratory, drawing specimens from surgeries performed by such luminaries as Maurice Howe Richardson, MD 1877, Arthur Tracy Cabot, MD 1876, and J. Collins Warren, MD 1866. Warren in particular used Byrnes' prodigious skill to capture the vivid color of tumors from his cases, and her drawings are present throughout the scientific reports of the Harvard Cancer Commission, which Warren chaired.

Perhaps Byrnes' most innovative work at HMS was creating original drawings of transverse sections of a pig embryo for Professor of Histology and Human Embryology Charles Sedgwick Minot's 1903 *Laboratory Textbook of Embryology*. While never mentioning the artist by name, Minot stated that Byrnes' drawings demonstrated "a special degree of skill and considerable faculty of plastic imagination." To make the drawings, Byrnes collaborated with Frederic T. Lewis, MD 1901, then an instructor in histology and embryology. Supplied with hundreds of transverse sections prepared by Lewis, Byrnes reconstructed the pig embryos at enlarged scale using a microscope and camera lucida. Minot believed these reconstructions were highly useful for student study, given the small scale of the original specimens, and celebrated Lewis' histological achievement while generally ignoring Byrnes' artistic one.

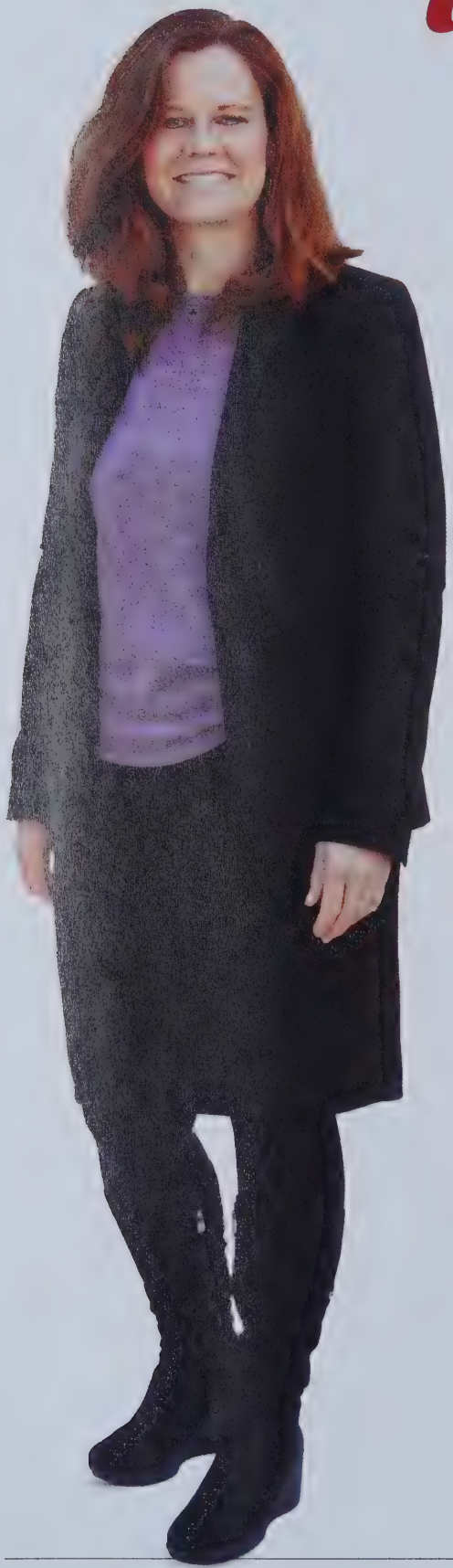
Drawing specimens under a microscope was a specialized skill of Byrnes'. A review of Alfred H. Gould's 1906 *The Technic of Operations upon the Intestines and Stomach* stated that Gould was "fortunate in securing the co-operation of Florence Byrnes whose beautiful histological drawings illustrate the first chapters of the book. . . ."

Byrnes' career at HMS ended in 1907, when she received the ultimate academic compliment; she was hired away by the Mayo Clinic's Louis B. Wilson, who had observed her work in the HMS laboratory of Harold C. Ernst, MD 1880. Despite being a contemporary of celebrated medical artists like Max Brödel and H. F. Aitken and preceding the Brigham's Mildred Codding at HMS, Byrnes remains relatively obscure. However, one of the historical benefits of being a skilled artist is that your work endures. Beyond the original pieces in the Warren museum, HMS' publications from the turn of the twentieth century frequently demonstrate Byrnes' discerning eye and steady hand. *—Dominic Hall*

Dominic Hall is curator of the Warren Anatomical Museum in the Center for the History of Medicine at the Francis A. Countway Library of Medicine.

in 5

A conversation with Ann Partridge, vice chair of medical oncology; founder and director, Program for Young Women with Breast Cancer; director, Adult Survivorship Program; and senior physician, Dana-Farber Cancer Institute; and professor of medicine, HMS



Why does the interplay of psychosocial and behavioral factors in breast cancer interest you?

I am infinitely interested in the human experience. It's fascinating when you listen to a patient and realize breast cancer may not be their biggest problem; they may be worried about whether they're going to feed their children next week, not about something that could come back in ten years. Teasing those things out is important to caring for the individual.

Why medicine, why oncology?

My father is a physician, so I was brought up on medicine. In college, I was kind of a student of life. I tried to explore other avenues, to make sure I wanted to do medicine and not just follow in my dad's footsteps because he is my hero. I looked into other majors, but I couldn't not do medicine. I was drawn to both the science of it and the patient care aspect of it. In the end, I felt medicine was too compelling to not do it. I've never looked back.

What are some of the unknowns about breast cancer that continue to mystify researchers?

Why do some cancer cells become resistant to our best therapies, how can we prevent this, and how can we develop therapies that overcome it? Continuing to figure out what's going on at a cellular level as well as globally within the host is critical. How can we better risk-stratify patients so that we can spare patients therapies they don't need? With good intentions, in breast cancer, we often overtreat the many to help a fraction. We are learning how to better select the patients who will benefit from a therapy, and we're also working to create therapies that are less toxic and more targeted. Finally, how do we better employ the effective treatments we already have? That's where you get at the behavioral psychoemotional aspects of cancer care.

What is a hard choice you've had to make as a physician-scientist?

There are so many interesting and important things to pursue but I think the hardest thing is choosing to do something risky, recognizing that often scientists and doctors are conservative by nature. But the best scientific work, the best research, is by definition a little risky.

Considering the pain and stress of your work, how do you recharge and prevent burnout?

Doing research helps; it makes you feel that even though you couldn't fix one person's problem today, you're working to fix problems more globally. Another is being a researcher at a place like Dana-Farber: You know in your heart that if you and the studies and the support you have here couldn't fix a patient's problem, then probably nobody could have. If I lose a patient, I often say, "I so wish we could have done more, but I am going to continue to work so that we can do more to prevent these tragedies." Finally, you have to take care of yourself. You've got to make sure you're sleeping, eating, taking time for your family, your friends, your dog—and yourself.

—Ekaterina Pesheva

JOHN SOARES DONFIORE/ISTOCK/GETTY IMAGES (FACING PAGE)

Shop Talk

A physician-neuroscientist explains cellular communication and its role in human health and disease

by Jonathan Lieff

THE SECRET LANGUAGE OF CELLS describes multiple kinds of cellular conversations. Cells talk about every aspect of life—where they should be in an organ, what time of day activity must occur, how big they should grow, how they can fight microbes together, how to rebuild and heal tissue, and how to cooperate to provide necessary functions for our daily activity. Conversations determine types of inflammation, how food is digested, and chronic pain. Almost every aspect of physiology is determined by back-and-forth signaling among groups of cells. Often, the discussion group is large and includes blood cells, tissue lining cells, immune cells, and brain cells, all at the same time. …

Cells know the time of day

Every cell has its own clock, and each type of tissue has its own specific set of internal clocks. Signals from the central brain clock coordinate physiological functions, such as metabolism and immune responses, with clocks in cells and tissue.

Single cells coordinate with the brain's central clock as it responds to light and darkness cycles, bodily movements, and cycles of eating and fasting. Genetic loops in individual cells create oscillations that sync with other bodily rhythms. The brain coordinates and plans for specific activity related to the environment with these signals. Signals from the central brain clock to all cellular clocks anticipate the major activities of the total organism, such as eating and sleeping.

The first individual cell clock in evolution was developed in bacteria two billion years ago, and this was based on sun availability. In addition to enabling these bacteria to produce energy by photosynthesis, sun rays break DNA. At the same time, most cellular DNA repairs occur when the sun is bright. The first clock allowed microbes to plan ahead with resources for DNA repair when the sun was brightest.

This colored scanning electron micrograph of a human blood clot forming shows threads of fibrin protein (yellow), red blood cells, and spiky platelets.

Clock mechanisms and signals are complex and not yet fully understood. A mechanism in the gut that coordinates the cycles of two cells was discovered recently. Friendly microbes living near gut cells move in a timed pattern—a micrometer to the left, then right, then back. Back-and-forth signals from each position keep the microbes in sync with the cellular rhythms of the nearby gut lining.

An individual cell's clock mechanism is based on timed feedback loops of interacting genes. Clock genes, components of the body's internal timekeeping system, are both stimulated and inhibited by RNA and protein molecules. A gene is triggered, producing a protein or RNA, which then triggers a second gene in the circuit. The second gene product stimulates a third gene, and so on. These events form a cycle that lasts twenty-four hours.

Molecular tags are an important type of signaling device … Tags placed on proteins to protect DNA are also part of these clock loops. Tags can open or close the availability of particular genes that produce RNAs and proteins related to clock functions.

While all cells have the same basic genetic clock machinery, various RNAs and proteins specific to each type of cell and organ are signals that produce various clock functions. A huge amount of all RNAs—at least 10 percent—are related to tags and signals for clocks. Multiple layers of genetic regulation influence these cycles. For example, very recently a new form of regulation was discovered that alters three-dimensional structures of the DNA molecule in the nucleus. When the structure changes, it alters how physically close particular genes are to each other. Bringing certain genes near each other can synchronize clock functions.

Multiple influences affect clock rhythms. Signals from metabolic cycles alter specific RNAs and proteins to influence clock genes. Various chemicals in particular organs affect clocks in different ways. Global factors, such as temperature and other environmental conditions, alter gene function. Many of these complex clock signals for individual cells are not yet understood.

When tissue cannot sync with the central brain mechanisms, illness can occur. One issue that needs to be addressed is our twenty-four-hours-a-day, seven-days-a-week online culture, which pays no attention to the rhythms corresponding to daylight that were established in our distant evolution. …

Platelets—much more than a plug

… Before the discovery of platelet conversations with immune cells, blood vessel cells, and tissue cells, it was hard to even imagine a platelet functioning as a cell. How could platelets manufacture signals and receptors and respond to situations without a nucleus and DNA?

In the fight against microbes, platelets also use special receptors.

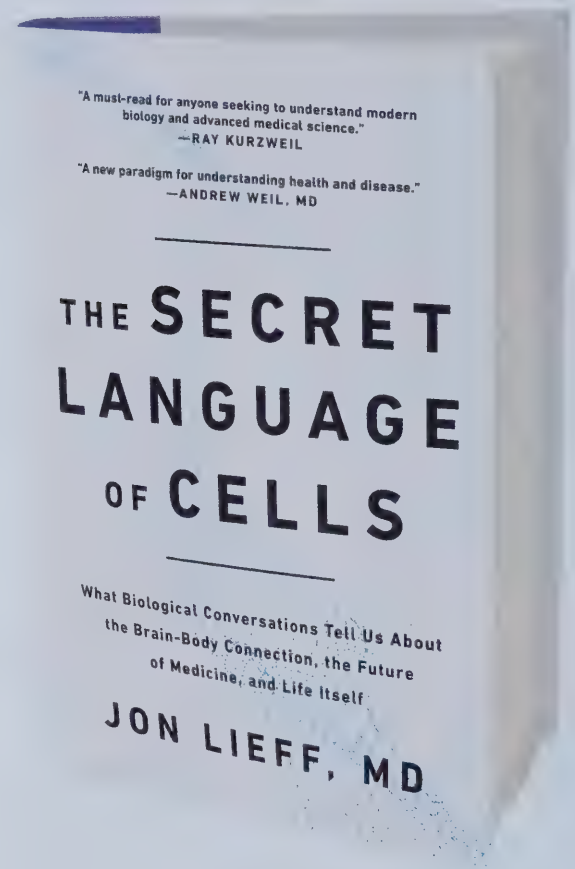
The answer is that they get what they need before they break off from their mother cells, large bone marrow cells called megakaryocytes. These mother cells supply platelets with a large repertoire of messenger RNA molecules, which is coded from their own DNA, as well as protein production machines called ribosomes. With all of this support, platelets are able to manufacture a full vocabulary of signals and receptors by themselves.

Platelet conversations are as vital and varied as those of most immune cells in their early responses to invaders and injury. Platelet signals are critical when defending against microbes, often being the first cells to encounter microbes in the body. Present throughout the blood in large numbers, platelets find microbes quickly and send messages to immune cells to stimulate defenses. Platelets call for white blood cells and actively participate with immune cells in fighting infections. They assist T cells in directing the B cells to make better antibodies.

As well as signaling to immune cells for defense against invaders and confronting microbes themselves, platelets tackle another difficult problem—blood dynamics. Stopping blood loss is not as simple as it seems. While they halt bleeding, platelets must also respond to each type of tissue's need for an exact amount of blood flow. Too much or too little blood will damage tissue. If the clotting is too great, it can become generalized throughout all of the blood and can damage multiple bodily regions at the same time. Without enough clotting, tissue will die.

As first responders to damage, platelets must immediately stop bleeding, keep blood flowing appropriately, and, at the same time, defend against microbes. At the moment of an injury, microbes enter tissue through paths of trauma or foreign bodies. Damage to tissue and blood vessels triggers cascades of blood clotting factors, which instruct platelets to change their shape for clotting. Platelets also send signals to attract immune cells for rebuilding tissue and help mold scaffolding molecules outside cells that form scars. Somehow, they engage in all of these activities simultaneously. …

Only mammals have platelets. Other creatures use different blood cells for the same work. As just mentioned, platelets are produced by megakaryocytes in bone marrow. Responding to signals from the liver and kidneys, megakaryocytes grow twenty times larger just before they produce thousands of platelets, which live for about a week. Mother cells travel from bone marrow and are stored in the spleen for emergencies. They are released by signals from neurons. Wide-ranging conversations keep the necessary supply of platelets, but not too many.



Platelets can change shape rapidly because they are wrinkled, with a large amount of extra membrane tucked into folds. Messages from other cells tell them when to alter their shapes. Inside the platelet, scaffolding molecules respond and produce many long arms, stretching from the platelet's body. Platelets change shape in three stages—multiple new arms and legs, a spreading body, and a thicker center. Motors just below the membranes rapidly increase the membrane surface area without needing to stretch or add new material. Arms then attach to breaks in blood vessels. After that, multiple platelets join their arms together to form a plug.

Platelets produce messages and attack molecules sent via sacs filled with chemicals. Platelets only use these sacs when they have changed from being round to having arms. Sacs contain three kinds of signals, each with multiple varied effects. One type regulates blood flow. A second type attaches and kills microbes. A third remodels clots to help heal the damaged organ. To kill microbes, platelet arms grab them and inject sacs. Platelets have a wide range of receptors to sense each type of microbe, and they have specific toxic chemicals to kill each species. …

Platelets can sense the type of injury and its exact location, and they move rapidly to the site. Because there are many more platelets than other blood cells, platelets become the most abundant player at the trouble spot while they wait for more powerful T cells and neutrophils to arrive. When platelets sense a microbe, they change shape and release molecules for attack.

To fight microbes, platelets use various techniques. For one difficult bacteria species, platelets release multiple different sacs, some with phosphate energy particles and others with proteins that use these same energy particles to attack the microbe. Bacteria respond to the attack with their own signals that block the platelet secretions and break down platelet proteins. Platelets then secrete enzymes to break down the bacterial attack proteins. This battle of back and forth attacks continues in various forms. …

Platelet secretions used against microbes can serve multiple purposes at once. One enzyme known to initiate the clotting process has been recently found to also cut pieces of a platelet product into multiple fragments, each designed to target specific microbe species. Another multipurpose molecule from platelets has varied sections and modules that evolve as microbes change. Distinct regions of the molecule signal to other cells for help and kill microbes of various types. Signals can call for reinforcements as the platelets are directly attacking the microbes.

In the fight against microbes, platelets also use special receptors. Internal receptors can sense how many attack molecules they have left. When needed, signals are sent internally to mobilize messenger RNAs and ribosomes to produce more attack molecules, sometimes increasing production by a factor of a hundred. Receptors also allow platelets to distinguish membranes of human cells from those of microbes by analyzing specific fat molecules sticking out from both cells. In this way, platelet attacks can focus on killing only microbes, not human cells.

The large number of platelet attack molecules is effective against a wide variety of microbes, including bacteria, fungi, protozoa, and many viruses. Recently, platelets were shown to be a critical first line of defense against HIV (human immunodeficiency virus). Platelet factors have been shown to limit strep heart infections. One specific platelet molecule attacks parasites that cause malaria by entering the red blood cells where the microbes have taken over. Research shows that the more platelets in the body, the better the chance against malaria. Platelets are also effective against a variety of fungi. To attack worms, platelets produce hydrogen peroxide and other attack molecules. Platelets can't eat microbes, but they can hold them off till the bigger scavenger cells arrive to consume them. …

Jonathan Lieff, MD '72, is a neuropsychiatrist who specializes in the treatment of elderly, medically ill, and brain injured patients. He was president of the American Association for Geriatric Psychiatry and a founder of the American Journal of Geriatric Psychiatry. *This excerpt is taken from his 2020 book,* The Secret Language of Cells, *and is reprinted with permission from BenBella Books, Inc.*

MAYA RUCINSKI SZWEC, STEVE BOXALL (FACING PAGE)

Legacies

HE STARTED OUT MAKING EYEGLASSES. Today, he builds genetic pedigrees. According to Alan Shuldiner, the two pursuits are linked: that first job in his father's optometry practice helped instill an interest in medicine and hone the people skills he puts to use in his genetics research among the Old Order Amish in Pennsylvania.

In the 1980s, Shuldiner became captivated by endocrinology, "the most molecular of all the medical disciplines at the time," he says. The interest blossomed when, following a fellowship in endocrinology at the National Institutes of Health, he landed his first faculty position at Johns Hopkins School of Medicine, in the geriatric medicine and gerontology division.

But a curiosity about genetics began germinating after Shuldiner had the good fortune to connect with a senior faculty member, Victor McKusick, widely considered the father of medical genetics. McKusick had done foundational work among the Old Order Amish studying rare single-gene diseases.

Shuldiner pitched a research project on diabetes in the Old Order Amish, and McKusick, seeing the value in his young colleague's proposed work, introduced Shuldiner to Sadie Beiler, an Amish woman who was one of McKusick's research liaisons.

"Sadie said two things that focused the rest of my career—that she had diabetes and 'up here' diabetes runs in families," Shuldiner recalls. "Ultimately, beginning with Sadie's help, I was able to construct huge Amish pedigrees. That not only began my genetics career but also led to the establishment of the Amish Research Clinic in 1995."

Studying diseases of aging in what is known as a founder population—an isolated population descended from a small close-knit group such as the Amish—has yielded discoveries that apply to the general population as well.

His life and his career, Shuldiner says, have been strongly influenced by his time at HMS. An alumnus of the Harvard-MIT Program in Health Sciences and Technology, he speaks of the great friends he made during days spent working together and taking the bus to and from Vanderbilt Hall and MIT.

Michael Rosenblatt, MD '73, whom Shuldiner met while a first-year at HMS doing a research stint at Massachusetts General Hospital, has been "a fantastic mentor—a lifelong mentor. He is really a major influence on my life."

Shuldiner also cites former HMS Dean Joseph Martin as an influence from his training at Mass General. "Joe is Mennonite, and I've come upon him many times up in Lancaster when he'd be invited to talk about his Mennonite roots and how he became a physician and ultimately dean of HMS."

Most gratifying for Shuldiner now is his work in translational medicine—taking basic science discoveries into "something real." He says he "likes to bang a drum about opportunities for collaboration and synergy between academia and industry."

—Susan Karcz

Alan Shuldiner, MD '84 | vice president, Regeneron Genetics Center | John L. Whitehurst Professor of Medicine, associate dean and director, Program for Personalized and Genomic Medicine, University of Maryland School of Medicine

Student Life

Shivangi Goel

FROM AN EARLY AGE, fourth-year medical student Shivangi Goel knew she wanted to pursue a medical career, in large part because of the biennial visits she made to India with her parents, who immigrated to New Jersey in the early 1990s.

As an only child, Goel is extremely close to her parents, and also, thanks to the frequent trips to New Delhi, to aunts, uncles, cousins, and grandparents who live there. "There was no doctor in my family," she says, "so I wanted to be the person who could fill that need."

Her resolve was strengthened by her own experiences with the medical profession. "When I was younger I was sick a lot," she says. "I grew up going to doctors' offices, getting blood tests, going to specialists. I saw the power health care providers can have on a family, how they are able to provide peace of mind and help people feel better not just physically but mentally."

By her junior year of high school, Goel was getting practical experience in the field by working as an emergency medical technician in Paramus, New Jersey. "It was a little out of my depth," she admits, citing calls for drug overdoses, alcohol intoxication, gun violence, and multi-car highway accidents. "I delivered a baby by myself when I was 16. But when someone's having an emergency you need to show up calm, confident, and ready to help. It helped me become more sure of myself and to see how I could be valuable to society."

As an undergraduate at MIT, Goel explored neuroscience, economics, biological and mechanical engineering, and computer science, switching majors "about five times because I loved everything so much." She finally settled on a dual degree in biology and political science, with a focus on health care economics. "I'm interested in the intersection of health care, policy, and technology," she says. "That led me to Harvard. At HMS people want to make systemic changes in how health care is delivered and accessed." Her desire to work on "initiatives for students and the larger community" led her to run for, and become, class co-president. Her ultimate goal, "to focus on health care access through technology," led her to the MD-MBA program.

Goel looks forward to combining her clinical and engineering background with her MBA to develop medical technology, either through leading research projects for the government or running her own company.

"I don't just want to work with one person at a time," she says. "I want to help change the face of how medicine is delivered to make care better and more accessible for all patients."

—Elizabeth Gehrman

KELLY DAVIDSON (THIS AND FACING PAGE)

Nicholos (Nicky) Joseph

THIRD-YEAR STUDENT NICKY JOSEPH wasn't always sold on medicine. "It's not that I don't like science," says Joseph, who is also president of his HMS class. "I've just always loved math more."

When he was a kid, Joseph's dad taught him various "math tricks," and his parents eventually enrolled him in an extracurricular math-enrichment program where he rose to the tenth-grade level by age 8. Joseph discovered contest math in sixth grade and got so involved with it that in high school he served as president of the school's Math Honor Society. Later, with his college roommate, he co-founded a contest program in Houston city schools called Power in Numbers.

Still, even after an undergrad organic chemistry course at Rice University showed him "the intersection of math and science," he wasn't sure where his passions would lead him. He didn't put two and two together, so to speak, to arrive at the idea of med school until he'd volunteered in the pediatric cancer wards of Texas Children's Hospital and did a service trip to a Ronald McDonald House in Atlanta.

"I saw resilience in children that I hadn't seen in anyone else," he says. "I was marked by the experience and felt that serving pediatric patients would be fulfilling and also allow me to make an impact in the world."

It wasn't Joseph's first experience helping children. His parents, immigrants from India, both "worked two jobs pretty much their whole lives to support me and my siblings," he says. "I'm so appreciative of that, but it meant in some ways I was forced to grow up early to help take care of my siblings."

Joseph discovered he had a natural proclivity toward working with children, especially those in their early years. The experience, he says, "made me want to understand the effect of the parent-child relationship on development, and to become involved in pediatric care."

So his path forward is clear, right? Not necessarily. "I don't want to give up the care of adults," he says. "I'm also drawn to emergency medicine." A summer job at the U.S. Agency for International Development during college showed him the value of policy work in action on a global scale; he hopes to start pursuing an MD-MPP next year. "We as a society don't just have to make medical interventions," he says. "We also need to change policy."

He's not sure whether his interest in policy will lead him toward research, international development, or hospital administration, but he knows it will be part of his future. "Getting involved in policy and decision-making will allow me to have an effect on an even larger number of people," he says.

Can't argue with that math.

—Elizabeth Gehrman

KELLY DAVIDSON

Derek Soled

EVER SINCE MIDDLE SCHOOL, Derek Soled has been determined to do as much as he can, as well as he can, not to satisfy his ambitions so much as to create a good vibe for himself and those around him.

"I get pure joy from it," he says. "I find I'm happiest and feel like my best self when I'm surrounded by the people I care about who are doing good things and achieving. And in order to make people around me their best selves, I have to be the best I possibly can be, too."

Soled, a fourth-year student and class co-president, says he was "naturally very driven," and that his upbringing reinforced that tendency. "My mom and dad didn't pressure me but they always prioritized education and found meaning in life from being around other people." Twice a year Soled's parents took him and his two younger sisters on short-term cultural immersion trips to developing countries around the world, and it was while playing soccer with kids in Tunisia and visiting schools in Ecuador that he developed his interest in medicine.

"I met people with disabilities or ailments that would not have held them back in the U.S.," he says. "I began to see health as a great equalizer."

As a Yale undergrad Soled double-majored in sociology and biology because, he says, "social and biological influences together determine health outcomes and disease trajectories." He was also captain of the fencing team, chair of the journal *The Politic*, and vice president of the debate society, among other activities.

At Harvard, Soled is again pursuing a joint degree, this time in business and medicine. He continues to fence and has picked up his beloved trumpet again, doing occasional gigs around Boston. In his first year he co-founded, with three classmates, Medicine in Motion, a nonprofit that brings health care professionals together through physical activity. It now has chapters in fourteen states and five countries. He wanted to become a leader of his HMS class, he says, because "I'm surrounded by such impressive and amazing people here, I wanted to get to know them better."

He hopes that combining his MD-MBA with the masters he earned in medical anthropology at Oxford will allow him to "help create stronger health systems through policy, public health delivery, and innovation." Why? To help people become the "best versions of themselves," of course. "It all comes down to leveling the playing field so that poor health is never a ball and chain for people trying to realize their goals," he says.

As for realizing his own goals, "I've always felt that if I didn't achieve something it was due to a lack of effort rather than a lack of understanding or innate ability," he says. "So, therefore, everything is in reach." —*Elizabeth Gehrman*

Before the pandemic made working from home the norm, food trucks regularly visited the campus, bringing with them a variety of sought-after fare.

Restaurant **Tour**

Michelin, schmichelin. We had *The Weekly Murmur*!

by JiYeon Kim

LAST SUMMER, AS THE GLOBAL PANDEMIC raged through Los Angeles, I decided to sort through boxes in my attic. Among the mementos I stumbled across were twenty issues of *The Weekly Murmur: Tracings of Student Life*, a newsletter published at HMS from October 2003 to April 2004. Reading them, I was touched, delighted, and amused; the articles were informal snapshots of my HMS and Harvard School of Dental Medicine classmates and captured our last year together prior to scattering to our clinical clerkships. As far as I know, the cache I found is the only remaining physical copy of this series, and I suspect my chief reason for saving them from the recycling bin was my nostalgic attachment as the publication's editor-in-chief.

While there had been previous iterations of student newsletters, some going by *Murmurs* or *Rounds*, none were circulating by the time I arrived at the Longwood campus in the fall of 2002. My own inspiration for dispatching a communication at an ambitious weekly pace was not from any high-minded literary aspiration, but rather a prosaic need for a guide to free food on campus. I had started my second year with sore memories of spending my first year haplessly roaming the hallways of the Tosteson Medical Education Center trying to track the source of savory smells by listening for nearby whoops and cheers from lucky bystanders. The bevy of posters taped to the doors and columns in the TMEC atrium proved to be a poor resource, as they became outdated quickly—or were smothered by competitors. Other students voiced similar frustrations over narrowly missing any delectable meal opportunity, while concurrently, student organizers despaired of filling their rooms with attendees. With an altruistic desire to solve our problem of food waste, I recruited several of my classmates, all enthusiastic and gifted writers and editors, to contribute content to what I envisioned would be a single-fold, four-page weekly publication that would feature relevant refreshments in the upcoming week's list of student events on its back page.

To the table

Food was reliable coinage for coaxing our diverse and independent-minded student body to serve as an audience outside the classroom, and quickly established our readership. From a class of 165 students, we had 165 future leaders in medicine and dentistry, or so we were told. This message likely fueled the high ratio of student-led organizations to number of students on campus. Interest groups, teams, and charities cheerfully vied for our attention by offering enticing hot or cold foods at their events.

We made room for them all on the back page.

There was "lunch provided" at the Music Society's first meeting on Monday, as well as later on Thursday for "Beautiful Day in the Neighborhood: Structured Violence, Service and the New Community Medicine." You could have a "free Indian food lunch" while sitting in on a talk on "Yoga Research and Therapy." I am still entranced by titles such as "How to Deliver a Baby on an Airplane with Your Shoestrings and a Newspaper," sponsored by the Low-tech Medicine Interest Group, which included a "non-pizza" dinner, and the reception and photo exhibit, "Don't Turn Away, Life in Countries Affected by AIDS," presented by the Harvard Medical Student AIDS Action Initiative.

Critical reviews

Other sections of the newsletter reflected the personalities of their contributors. The "Opinion" and "Topical" columns, edited by Martin Schoen, MD '06; Mario Luis Ramirez, MD '07; and Jason Sanders, MD '08, captured the often humorous or poignant observations and rants we expressed as we tried to work out our places as the newest members of a hallowed profession and institution. In one of these columns, Jennifer Broder, MD '06, considered how we could maintain empathy as physicians when the "initial reaction to pain and sadness is to try to protect ourselves by creating distance between ourselves and our patients." In another, Joseph Wright, MD '07, described an experience prior to medical school of enjoying a "delicious, subtle, creative, and spicy" meal that included a "spectacular crispy fish that changed my mind about crispy fish," while also channeling the evolving ethics surrounding drug company-sponsored dinners. Felipe Jain, MD '08, used another column to rebut a prominent Harvard administrator's statement that U.S. trade policies had no direct bearing on the public health crises of AIDS and malnutrition in Africa by pointing out that at times tariffs cost "$100 billion, or more than twice all development aid," and the interest due on national debts was "equal to or more than that allocated for health."

Sparr's Drug Store (shown here circa 1960s) once stood at the corner of Huntington and Longwood Avenues. Its lunch counter and soda fountain were frequented by many in the Longwood area during the nearly seven decades it was in business.

A theme opined on frequently in these columns was the changing nature of our curriculum, which seemed to exist in a constant revisionist state. We went from flexing our ability to memorize facts to learning patients' life stories, and later, trying to determine the merits of sequential versus longitudinal clinical rotations; members of our class volunteered for the first of such innovative tracks. Schoen worried that dry subject matter like biochemistry would lose "human context" without clinic time, citing a compelling case study of a woman who "exercised over 10 hours a week and painstakingly documented every detail of how much she ate, yet continued to gain weight despite being over 200 lbs." Christopher Russell, MD '07, responded to first-years

HARVARD MEDICAL SCHOOL

Join us in our work to alleviate suffering and improve health and well-being for all

HMS.HARVARD.EDU/HM-GIFT

PLEASE PLACE STAMP HERE

HARVARD MEDICAL SCHOOL
ALUMNI AFFAIRS AND DEVELOPMENT
P.O. BOX 419720
BOSTON, MA 02241-9720

HARVARD
MEDICAL SCHOOL

TO GIVE

ONLINE at hms.harvard.edu/hm-gift
PHONE 617.384.8626 or 800.922.1782
CHECK *(payable to Harvard Medical School)*
CREDIT CARD *(details below)*
JOIN THE DEAN'S COUNCIL
with an annual gift of $2,000 or more*

ENCLOSED IS MY GIFT TO HARVARD MEDICAL SCHOOL OF:

☐ $2,000 ☐ $1,000 ☐ $500 ☐ $100 ☐ OTHER _____

DONOR NAME *MR. MRS. MS. DR.* _____ CLASS YEAR *(if applicable)* _____

ADDRESS _____

CITY, STATE, ZIP _____

DAY PHONE _____ EMAIL _____

THIS IS A: *(check if applicable)*

☐ JOINT GIFT _____ SPOUSE/PARTNER

☐ MATCHING GIFT
MY COMPANY (OR SPOUSE/PARTNER'S COMPANY) WILL MATCH MY GIFT. I HAVE NOTIFIED THE COMPANY OF MY GIFT TO HMS.

PLEASE DESIGNATE MY GIFT TO:

☐ **Where it is needed most**
☐ Therapeutic innovation
☐ Campus revitalization
☐ Cutting-edge research
☐ Financial aid and education
☐ Diversity and community
☐ Global health and service
☐ Other _____

CREDIT CARD GIFTS:
To make a gift by credit card, please do so **ONLINE** at **HMS.HARVARD.EDU/HM-GIFT**

MONTHLY RECURRING GIFTS AND PLEDGES:
To make a monthly recurring gift or a pledge payable over multiple years, please call 617-384-8626 to learn more.

PLEASE CONTACT ME ABOUT:

☐ Naming a chair in the Joseph B. Martin Conference Center Amphitheater
☐ Exploring naming opportunities with a gift of $25,000 or more
☐ Leaving a gift to HMS through our will, retirement plan, or donor-advised fund

M2124

** Recent grads can join the Dean's Council with annual gifts totaling $250 (1–4 years out from graduation), $500 (5–9 years out), or $1,000 (10–14 years out)*

DO NOT WRITE BELOW THIS LINE

fretting over the increasing difficulty of course exams by asking, "is a curriculum that expects more from students a burden or a service to students?" given the exhausting breadth of our collective extracurricular activities of "trying to change the world." Often, it felt as if we had inadvertently embarked on a form of extreme participatory research for training as compassionate and competent physicians and dentists. I guess more than fifteen years later I can accept the possibility that this interpretation of our experience could be both intentional and true.

With fork in hand

In any case, it was likely that none of us felt completely at ease with the yearly shifts in the pedagogy, and early side-eye comparisons were perhaps inevitable. We had already entered the School through two separate tracks—HST (Health Sciences and Technology; now the London Society), which cycled thirty students in classes at both HMS and MIT, and New Pathway (now Pathways), where the remaining 135 students received small group training as members of either the Castle, Cannon, Holmes (now Hinton), or Peabody academic societies.

Harry Potter jokes notwithstanding, small rivalries continued even outside the Society Olympics. Columns like "Survey Says," edited by Dorothy Weiss, MD '06; Thomas Kozhimannil, MD '06; and Vanessa Henke, MD '07, and "HMStyle" by Heidi Goodarzi, MD '07; and Yetsa Tuakli-Wosornu, MD '07, delicately and humorously exposed these divisions while giving a voice to dozens of students on campus. A survey on gratitude during the holidays elicited responses like "I'm thankful that my one-month-old son hasn't peed on me yet while [I've been] changing his diaper," by James Olsen, our classmate in the dental school, while another on what was missed most from vacation included "having time to watch Oprah," offered by Tiffany Jackson, MD '07; "my bed," by Kelly (Tiger) Edwards, MD '08; and "someone else doing my laundry," by Anonymous. Meanwhile, "HMStyle" broadcast the stylistic and sartorial choices of one or more persons of interest on campus in swoonworthy detail, with photographic evidence to boot. I finally understand what it meant to look like "a little bit of Harvard and a lot of California rolled into one"—it involves a Brooks Brothers sweater and "grungy ... cargo shorts."

It was striking to me that so many of the topics from *The Weekly Murmur* are the same ones our society continues to probe and debate today.


Tracings of Student Life

the Weekly Murmur

November 3, 2003
Volume I, Issue 2

Our Evolving Curriculum

Opinion

Martin Schoen

On Clinical Education

Inside the Murmur

Kit Lo, MD '06, Yana Pikman, MD '07, and Sanders eloquently and persuasively reminded us that movies, books, and, yes, our own creative writing and photography held power and significance, through the material they presented in "Fresh Cut," "Bookworm," "Reviews," and "Arts." One poem, penned by Kai-How Farh, MD '09, reverberates with me even more now that I've felt this as a medical student, pathologist, family member, and friend.

"I like to think that you were only a guest. / You borrowed this body, learned what you could, / and when it was time, moved on. I hope you loved it, / I hope you learned as much here as I have."

"Leaving Longwood," edited by Mária Némethy, MD '07, and Ramirez, described epic adventures and food sagas throughout Boston and Cambridge. There was also a special edition splashed across two issues: "Cutting the Vandy Cord," referring of course to Vanderbilt Hall, our Longwood campus dormitory. The merits and demerits of nearby neighborhoods were hotly discussed. Charles (Ted) Lord, MD '06, memorably praised Jamaica Plain, the home of El Oriental de Cuba, where you could buy a "Cuban sandwich (smoked pork and ham) and a batida (tropical fruit shake; one flavor *Morir soñando* [or] 'to die dreaming.' Say no more.)" As a rejoinder, Wright enthused about Inman Square's Punjabi Dhaba, where "if a group of Punjabi truck drivers were to walk through the door, they'd have to order and listen carefully for their shouted-out numbers just like everyone else. Please don't make Mr. P. Dhaba shout twice... when people don't listen for their numbers, he gets this look on his face like he wishes he were somewhere very far away. Then he shouts out the number again. People! Listen for your number!"

One of my personal favorites for rereading has been "Eat Your Heart Out," otherwise known as our food recipe column, written by Allon Beck, MD '06. Describing his process for making potato latkes, he started by setting the tone, "there are differing schools of thought

"At El Oriental de Cuba, a Cuban sandwich (smoked pork and ham) and a batida (tropical fruit shake; one flavor *Morir soñando* [or] 'to die dreaming.' Say no more.)"

On a summery day before the pandemic sent HMS workers home, two visit one of the several food trucks that frequented campus (above). The tables and chairs along the wide sidewalks of the Quad (left) were popular spots for work and conversation in pre-pandemic days.

about latkes: some like them thick, some thin, some fine in texture, others coarse. Here is my favorite recipe: I believe latkes need to be simple, very finely textured, and wonderfully crisp. To achieve this, the potatoes need to be grated on a fine grater by hand, and they must be fried in very hot oil. Don't use olive oil—it doesn't fry hot enough, and you risk burning the oil." Another recipe for a "sumptuous hot drink" for "inner warmth" aptly notes that "the origin of mulled wine is shrouded in mystery, as is the origin of the word 'mull' in this context."

Today's fare

At some point on every nonholiday weekend, Sarun Charumilind, MD '07, Schoen, and I would face a daunting blank page on the computer screen and work to fill it with articles cajoled or extracted under mild duress from our classmates. What followed every time was an architectonic tour de force as three columns appeared with sentences wrapped neatly around photos taken by Keith Michael, MD '06. By the end of our tenure, we even had an online presence and dedicated email addresses, thanks to Michael Lu, MD '07, and Shannon McDonald, MD '09.

Malcolm Cox, MD '70, then the School's dean for medical education, and various faculty members encouraged us and weren't afraid to lean in to respond to our concerns on thorny topics such as rising medical student debt. Some would contribute their own original pieces. In hindsight, those latter topics were also highly relevant, such as an article by Deborah Anderson, then an HMS lecturer on medicine at Brigham and Women's Hospital, on the challenges of "nurturing women researchers at HMS." The Office of Medical Education and the HMS Student Council generously funded our work.

More than a decade later, it appears I may have unwittingly arrived full circle. I created and continue to act as editor-in-chief of a one-page newsletter from the laboratory and pathology departments, which is emailed monthly to more than eight thousand physicians who work with me at Kaiser Permanente Southern California. During the past year, this newsletter has been used to share key information about SARS-CoV-2 and innumerable related updates to our menu of laboratory tests.

I know we are far from solving any world problems with newsletters current or past. Even so, it was striking to me that so many topics from *The Weekly Murmur* are the same ones our society continues to probe and debate today, and likely tomorrow as well. My second-year self would ask whether there is a point to learning how to become a "compassionate and competent" physician or dentist when all the original problems remain unsolved. I suppose one answer might be contained in the narrative form known as the hero's journey, a series of templated challenges that end with a true and decisive transformation—of the hero. Perhaps, after all of this, we are at once a work in progress and an outcome by which our strivings can be measured. HM

JiYeon Kim, MD '07, a clinical pathologist, is the physician director for the esoteric chemistry, special coagulation, and immunology lab departments at Kaiser Permanente Southern California Regional Reference Laboratories, and provides strategy and oversight for the region's laboratory information systems.

JOHN SOARES (TOP LEFT); GRETCHEN ERTL

Nneka Azikiwe, MD '97, examines a patient as Leon Goldman, a former HMS associate professor of surgery at Beth Israel Deaconess Medical Center, looks on. This photo was taken in the late 1990s.

DETAILS, UPDATES, AND OBSERVATIONS FROM ALUMNI

What do you remember about your **first patient encounter?**

Laurie Green, MD '76

In our day, inpatient stays were long. As medical students, we had little to add to medical decision-making. However, we had the time by the bedside, and, in turn, the patients taught us humility and humanity. Gilda had lung cancer and died at 34, a nonsmoker with three children. Donnie had congenital heart disease and multiple cardiac surgeries. He lived in Lowell with his mother. I kept up with them until he died at 32. Forty-five years later, I still cherish his drawings and Gilda's locket.

Laura Holmes, MD '83

As a first-year medical student, I had a wonderful clinical preceptor, **Laurence Green, MD '72**, a cardiologist at the Brigham. My fellow student and I visited an elderly woman with heart failure and listened as our preceptor interviewed her. She denied all claims of chest pain or shortness of breath. Upon further questioning by Green, she disclosed that she sat in a chair or up in bed all day. Later, he told us that a successful clinician puts a patient's history into a practical context.

Tamara Fountain, MD '88

During OB-GYN rotation at the Brigham, I was assigned to be an overnight companion for a young expectant mother who was in premature labor and had no one to be with her. We both slept between contractions but talked about everything under the sun when we were awake. In the morning, her husband, having arranged childcare for their toddler at home, arrived to relieve me. I found out later she gave their new baby girl the middle name Tamara.

Samuel (Bob) Snodgrass, MD '63

I examined patients from the second year on; in terms of doing something for patients I most remember putting patients in casts, reducing a dislocated shoulder, and sewing up simple wounds during my Brigham surgical rotation. I had no interest in going into surgery, but these experiences stayed with me.

Barry Pressman, MD '67

I was surprised how receptive the patient was to being examined by this obvious neophyte.

Ken Lin, PhD '08 MD '10

I had the fortune to get assigned to a very patient patient. My H & P exam must have taken no less than an hour, and it turned into a fun conversation with the middle-aged gentleman. He was an active marathon runner who had been admitted for cellulitis. He had been an ED nurse, so he gave me constructive feedback on my physical exam. The conversation I had with him did inspire me to run the Boston Marathon a year later.

Richard Sogg, MD '56

I remember being terrified, feeling inadequate to actually deal with a human being, even as one of our group of four leisurely sat on the bed with the patient! That student later became a dean at a dental school.

Peter Barrett, MD '60

I was a second-year student at HMS in the spring of 1958, assigned to the MGH for physical diagnosis. I can still feel the warm breeze as it came through the open windows of Bulfinch 2, where I met my faculty mentor on the open ward. After some general remarks, he pointed out a frail, elderly woman on the far side of the room. My task was to approach the patient alone and obtain a relevant history. No physical exam was to be performed.

My patient was sitting quietly on the side of the bed and appeared comfortable. I introduced myself and began to ask about her health. Struggling through a review of systems, I learned little except that she did not smoke. My attempts to obtain a family history resulted in a lengthy account about dozens of relatives; I was no longer in control. Notably, she had two older brothers who fought for the Union at Gettysburg and survived. One of her sisters 'caught the dysentery' and died, and her parents' farm had been damaged.

At this point my mentor, my savior, arrived. I could not tell him why the patient had been admitted but could point out that she had had two brothers who fought at Gettysburg.

In this 2018 photo, Chelsea Messinger, an MD-PhD candidate, meets with a patient in a Crimson Care Collaborative Clinic at Massachusetts General Hospital.

He asked me if I had noticed anything about the patient that could be of importance, even though I had not been asked to perform a physical exam. I had nothing to report.

Does she smoke? asked my mentor. I felt proud that I had pulled this important information from my patient and told him that she did not smoke. He then turned to my patient: Do you smoke? No. Do you use a pipe? Yes, she used a pipe regularly, a corncob pipe, which lay on the bedside stand. She complained that the nurses would not let her use it on the ward.

While taking care to not embarrass the patient, my mentor continued speaking to her and pointed out an obvious lump on her left lower lip. He also pointed out a subtle fullness on the left side of her neck.

I had missed my first diagnosis, but I learned a great deal about the need for observation as part of the patient encounter, and as a bonus, I learned a great deal about the Battle of Gettysburg.

Richard Moskovitz, MD '73

In our introductory course on interviewing, I was assigned to interview a renal patient. I proudly presented the detailed results of my interview. Then the instructor asked if there was anything else I'd noticed about the patient. Turns out he was quadriplegic—I'd failed to notice that he hadn't moved throughout the interview.

Joseph Savino, MD '84

It was an AIDS patient, surrounded by the unknown and fear; HIV-1 had not yet been identified. We entered the patient's room in "astronaut suits," because we were going into a room with a disease we did not understand. The health care providers were frightened, fearful of contracting whatever it was. I can only imagine how frightened the patient was. A lesson learned long ago, apropos for today.

Kara Wong Ramsey, MD '09

It was with an elderly patient and my preceptor in my preceptor's primary care practice. I remember wearing my white coat with pride as I began my interview and feeling like a "real doctor." I tried to be thorough in my physical exam as we had learned in our didactics, textbooks, and videos, not wanting to miss any small thing. I think the patient was amused by my enthusiasm. I think of that thrill when I precept my own medical students now and see their joy to be at the patient's bedside.

Martin Prince, MD '85

It was an elderly patient with basal cell carcinoma of the nose, who was in the midst of a reconstruction procedure where skin from the chest was being brought to the face. He could not really talk to me because his face was tethered to his chest. It was tough to figure out what was going on.

George Hill, MD '57

It was in physical diagnosis, at the MGH. We had been taught to take a careful history of the present illness, a history of past illnesses, including childhood diseases, and a review of systems. Our group of four second-year students was shepherded by a surgeon, **Frank Wheelock, MD '43**. He asked each of us individually to examine one of his patients. When three of us had finally finished, **Bob Rivers** went in and immediately came out. He made the diagnosis immediately, and later became a great surgeon.

Richard Burney, MD '69

On the morning of Monday, December 4, 1967, I reported to Boston City Hospital to start the Principal Clinical Year. I was on Peabody 2, the women's ward. I wrote in my journal at the time: "My first night on call was truly surrealistic. During the course of the evening we had in close succession an acute pulmonary embolus causing ventricular tachycardia, an uncontrollable woman in DTs with a fever of 103 on whom we had to do a lumbar puncture, and a lady with dementia who had aspirated her dinner. It was unreal. It was quite a start."

Karen Singer, MD '77

I remember the humanity, actually being with a person who was generous enough to allow a student to interview them.

Peter Schrag, MD '64

Joel Rutman and I were classmates and partners in the course on physical diagnosis. We examined patients at Boston City Hospital in 1960 as second-year students. At first, we were lost, but slowly we got better. Joel and I had some good laughs and now in our old age we correspond by email between New York and Israel.

George Lewinnek, MD '67

My father was a family doctor. My first encounters were watching him treat patients. When I was in college, I sat in the kitchen of an elderly man who had developed diabetes. My father explained the disease to him. I remember feeling disoriented; hearing about glucose seemed so remote when delivered in a lecture at college, but now it was being discussed in an everyday kitchen.

Jane Farhi, MD '81

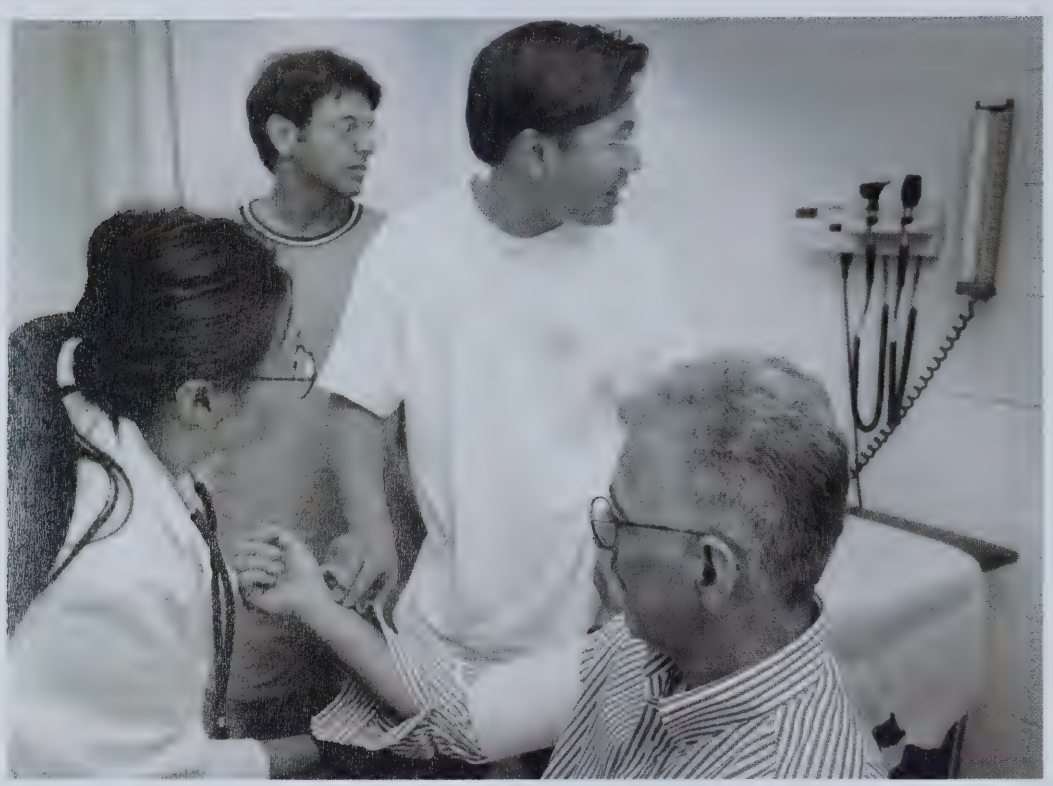
My first day as an intern was overwhelming. I was at Elmhurst Hospital, a Mount Sinai affiliate, and nothing at HMS had prepared me for how sick the patients were. Two out of three died and the third, a patient from a psychiatric hospital, had viral meningitis and rhabdomyolysis with acute renal failure.

Peter Zawadsky, MD '68

My first encounter occurred at Boston City Hospital during the Introduction to the Clinic rotation. The patient was a middle-aged man who had developed mitral stenosis as a complication of acute rheumatic carditis. This was my first experience listening to heart murmurs. **Larry Seidl Sr., MD '61**, was my instructor.

Priscilla Slanetz, MD '91

My first encounter with a patient was with a prisoner admitted for bipolar disorder. My preceptor chose me to take a history during Introduction to Clinical Medicine. It was then I realized that I had an ability to connect with people. Even after the patient told me that he hated people with my first name, I remained calm and managed to get him to tell his story. I felt uneasy throughout but took comfort in the fact that two armed guards were nearby just in case the patient lashed out at me.



The two young men in this 1998 photo are being instructed on how to obtain a person's pulse rate and blood pressure.

Steven Jacobs, MD '80

The first patient I examined in the physical diagnosis course was a woman who'd been admitted with some sort of GI symptoms. Upon examining her rather obese abdomen I palpated a firm mass in her left lower quadrant that had not been reported. Excitedly, I brought in my attending, who palpated a similar mass in her right lower quadrant. I was so jazzed and started thinking about the differential diagnosis. My attending then told me that the masses were her anterior superior iliac spines.

Sheila Hafter Gray, MD '58

My first patient was the cadaver I shared with three others in first year. I can still envision him. Finding the cause of his death was, as my current students say, awesome.

Richard Burney, MD '69

At the time, this is what I recorded: "On Friday, January 20, 1967, we were welcomed into the fold of clinicians as Physical Diagnosis got off to a start. It was the mystical laying on of hands … when we see a patient now, we can say, 'Good morning, I'm Dr. … '" It was a joy not to go to lab but to walk out of lecture and into the fresh air and look forward to putting in some "real time" with people. A person with a disease is inherently much more interesting than the disease itself.

Robin (Gottdenker) Smith, MD '88

One of my early patients was at the VA Hospital. He was described as a grouchy man who rarely let medical students draw his blood. Turns out he loved baseball, and I learned early on that if I checked the baseball score before going to draw his twice-a-day levels that he relaxed and told some great stories, which I still remember today. Patients are people first.

Mary Flowers, MD '78

I remember having sweaty palms and sweat dripping down my forehead! I was fresh from the segregated South and had suffered through the integration of the school system. When I learned that Boston was rioting because of forced integration of the school system, I thought: Here we go again! I inhaled and thought that I would be kicked out of the room because of the color of my skin.

Karl Singer, MD '67

The first patient I remember was a man with numbness in his hands and deformities in his fingers. It was my first and last patient with leprosy. I think this patient was frequently presented to beginning medical students.

Blair Eig, MD '83

The first patient I saw was a woman experiencing back pain. I was embarrassed at how long I took, but the patient was incredibly appreciative of the attention to her concerns. At the end she revealed she was "Mrs. Mike" of Mike's Pastry, and she had cannoli brought over for the clinic. I realized then that no matter how much knowledge I was to gain, it was the compassionate approach to interactions with patients that would be the most important trait I could develop. And the cannoli were great!

Elizabeth Dreesen, MD '87

The first person I admitted as a clinical clerk in medicine, at MGH, was an AIDS patient whose name I still remember. He was scared and so was the team, myself most of all. I was scared of AIDS, scared of being a bad medical student, and most of all scared of failing *him*. He died of pneumocystis at 11 a.m. two weeks after admission. After the death and the death paperwork, my resident, **Deb Weinstein, MD '84**, sent me home for the day, which was perhaps the most generous act that I experienced at HMS.

Steven Swerdlow, MD '75

My first patient encounter was at Boston City Hospital, where I was assigned to take a history and do a physical of my patient and then report back to my instructor. Unfortunately, I was unable to rouse the elderly woman, who was lying in a bed in a large ward; I was concerned she had expired. My instructor was barely able to rouse her. I ended up with no history and no physical. I was very anxious already, and this was not a calming situation. I became a hematopathologist.

Thanks to all who shared recollections on your first patient encounter.

The next issue of Harvard Medicine *will carry your responses to the question:* ***Which clinical rotation made the greatest impression on you, and why?***

Responses can be submitted online: ***hms.harvard.edu/rounds****; via email: hmsalum@hms.harvard.edu; by phone: 617-384-8520; or by mail: Rounds, Alumni Affairs and Development, Harvard Medical School, 401 Park Drive, Suite 505, Boston, MA 02215.*

LIZA GREEN

Obituaries

1930s

1938

Hugh Tatlock, MD
February 16, 2005

1939

James M. Geiger, MD
September 5, 2001

1940s

1944

Kenneth R. Kaess, MD
January 16, 2021

E. Wayne Wilkins Jr., MD
December 20, 2020

1945

Robert L. Post, MD
January 26, 2021

1950s

1952

M. Donald Coleman, MD
December 1, 2020

Rial W. Cummings, MD
February 2, 2021

Buel K. Grow Jr., MD
December 11, 2020

E. William Hancock, MD
December 1, 2020

1953

German E. Malaret, MD
May 16, 2020

Jason L. Starr, MD
September 16, 1994

1954

Jerome M. Block, MD
December 18, 2020

1956

Arthur F. Amick, MD
November 27, 2020

John W. Grover, MD
February 10, 2021

John Keith Inman, PhD
February 25, 2021

Charles M. Radding, MD
October 20, 2020

1957

Daniel J. Claes, MD
June 7, 2018

John B. Herrmann, MD
March 5, 2021

David C. Marshall, MD
June 29, 2018

Jean-Paul Revel, PhD
December 4, 2020

Lawrence J. Schneiderman, MD
August 8, 2018

1959

Charles E. Burden, MD
December 26, 2020

David E. Klein, MD
December 31, 2019

Hugh H. Kopald, MD
November 20, 2020

Anton O. Kris, MD
March 11, 2021

Raphael H. Levey, MD
March 23, 2021

1960s

1960

Lawrence M. Fishman, MD
January 27, 2021

James C. Tankersley, MD
January 18, 2021

1961

David C. Lewis, MD
December 2, 2020

1962

Robert B. Howe, MD
November 14, 2020

1963

Eva R. Kashket, PhD
May 21, 2011

Kenneth B. Robertson, MD
November 11, 2020

Edmund Merriman Wise Jr., PhD
December 1, 2020

1966

Harold B. Hawkins, MD
December 31, 2020

Neil S. McNutt, MD
February 12, 2021

1967

Warren Sewall, MD
January 22, 2021

1968

David T. Harris, MD
May 17, 2011

1969

David S. Hodes, MD
November 9, 2020

Michael A. Passero, MD
January 6, 2021

Richard W. Reece, MD
November 8, 2020

1970s

1975

Martha W. Magoon, MD
November 16, 2020

1978

Matthew A. Movsesian, MD
April 12, 2020

1980s

1980

Marcia A. Gonzalez, MD
January 11, 2021

1982

Timothy N. Kaiser, MD
December 24, 2020

Tamsin A. Knox, MD
April 29, 2020

1983

Donald A. Schwartz, MD
February 1, 2020

1988

Lisa H. Lerner, MD
January 6, 2021

2000s

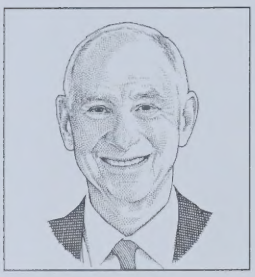
2002

Frank L. Acosta Jr., MD
November 21, 2020

This listing of deceased alumni includes those whose notices of death were received between November 20, 2020, and March 31, 2021.

PRESIDENT'S REPORT

Our **Sense of Purpose** Unites Us



THE HMS ALUMNI COUNCIL HELD ITS WINTER MEETING virtually on February 5. Despite our still being in the grip of the pandemic, the gathering seemed particularly energized.

We declared our experiment of inviting class presidents to join us a success. Current participants are the fourth-year co-presidents, Shivangi Goel and Derek Soled, and the third-year president, Nicholos (Nicky) Joseph.

Our conversation with Dean George Q. Daley, MD '91, is a consistent highlight. He provided updates on the pandemic: the student experience and the impressive contributions HMS is making, including to the development of two vaccines. Collaborations across the local-to-global spectrum have been key to the success of these efforts. And HMS faculty are assuming leadership and advisory roles in the Biden administration, extending the School's impact.

Daley also described antiracism initiatives being made on the Quad. Aligned with these efforts are plans for the upcoming reunion and the alumni day symposium. The latter, being planned by A.W. Karchmer, MD '64, chair of alumni relations, will examine health care, medical education, and systemic racism through the lens of the COVID-19 pandemic. The reunion and symposium, scheduled for June 3 and 4, will be virtual again this year.

Progress is being made on our main project of achieving a debt-free medical education for students with financial need. Lisa Boudreau, HMS dean for alumni affairs and development, told us about collaborative efforts with Harvard University's development office to obtain a transformative gift. Promising avenues have opened, but the effort is still in its early stages. This project is a marathon, not a sprint!

The debt-free medical education goal aligns with plans that president-elect Ken Bridges, MD '76, outlined for his term: a focus on mentorship and recruitment of prospective students from groups underrepresented in medicine. These are timely issues for HMS and medicine in the United States. The work will partner with that being done by other alumni and by the School's Office of Recruitment and Multicultural Affairs

A highlight of the Council's agenda was selecting the Distinguished Service Awardee. The award, now in its third year, is becoming established, and there has been a rapid growth in the number of nominees across class years and geographic area. Eleanor Gossard Shore, MD '55, was selected as the 2021 recipient. Daley will describe her contributions during the Alumni Day program on June 4.

Erik Gaensler, MD '84, chair of alumni giving, reported that alumni giving has increased over the past year and that the number of reunion donors is also ahead of last year's. The Council heard from a few members about their motivation for giving. The personal stories were touching and illustrated our links to the past and aspirations for the future.

As always, I invite you to send me your suggestions or comments. Stay healthy and safe!

Michael Rosenblatt, MD '73, is senior partner at Flagship Pioneering in Cambridge, Massachusetts.

Alumni Announcements

Distinguished Service Award for HMS Alumni

Congratulations to this year's winner, Eleanor Shore, MD '55. Shore, a former HMS dean for faculty affairs, is being recognized for her remarkable contributions to the School. In retirement, she has, among other volunteer efforts, helped the Center for the History of Medicine at the Countway Library collect, share, and celebrate the achievements of women in medicine; co-chaired and organized events to celebrate the seventieth anniversary of the matriculation of women at HMS; and, as part of the Shore Program team, helped support junior faculty who are pursuing academic work while they are assuming family or other responsibilities. Learn more at **alumni.hms.harvard.edu/service-award.**

Cast your vote in the Alumni Council election

This year's nominating committee has assembled an outstanding slate of candidates to serve on the Alumni Council. Votes must be received by noon ET on Monday, May 31. View candidate profiles and personal statements and access our secure online voting site at **alumni.hms.harvard.edu/election.**

Virtual Reunion

MD alumni from classes ending in 1 or 6 are invited to reconnect with classmates during Reunion activities starting June 3. This year's free virtual programs include social Zoom breakout sessions with students, a symposium on racial justice in medicine, and the dean's State of the School Address. Reunion committees are also organizing personalized events to bring classmates together. To view the latest updates and to register, visit **alumni.hms.harvard.edu/reunion.**

Virtual Alumni Day

Alumni Day is June 4 and features two virtual programs for all MD alumni. Sessions include the dean's State of the School Address and a symposium exploring health care disparities, biases in medical education, systemic racism, and social determinants of health care as viewed through the lens of COVID-19. For the latest details and to register, visit **alumni.hms.harvard.edu/alumni-day.**

MD Class and Master's Listservs

Want to share updates, initiate conversations, or simply be in touch with your classmates or fellow master's alumni? Private class listservs are available for MD alumni to connect with their HMS classmates. All class members are automatically included on these digital forums with the email addresses on file with Harvard University. To learn more, visit **alumni.hms.harvard.edu/connect.**

The Office for Graduate Education also has a dedicated email discussion group for graduates of the School's master's programs. You can join at **alumni.hms.harvard.edu/masters-listerv.**

RANDY GLASS

HARVARD MEDICAL SCHOOL

WHAT WILL BE YOUR LEGACY?

Consider investing in longer, healthier lives

A gift to Harvard Medical School through your will or trust is one of the simplest ways to leave a legacy. You can give cash or a specific asset such as real estate or personal property.

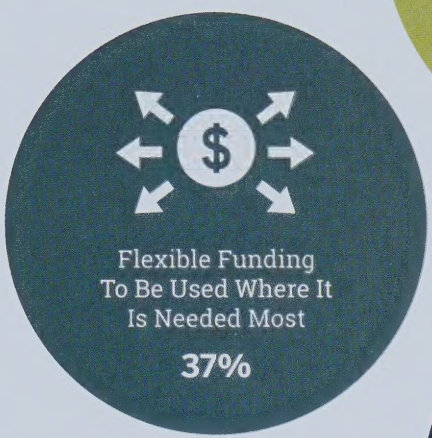
Bequest gifts of any size have had a lasting and powerful impact on the School, combining to provide more than $43 million in the past decade to alleviate suffering and improve health and well-being for all.

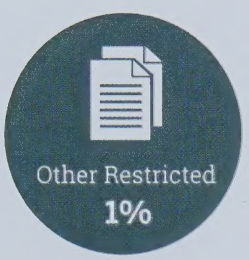
Benefits

- Fulfill your financial, tax, and estate planning goals
- Reduce or eliminate estate tax
- Improve health and well-being for all
- Create enduring impact at Harvard

Bequests

Since 2011, realized bequests have supported these key areas:





Learn more at
hms.harvard.edu/bequests

Or contact us in confidence:
Kate Murphy
1-800-922-1782
giftplanning@hms.harvard.edu

HARVARD
MEDICAL SCHOOL

25 Shattuck Street
Boston, Massachusetts 02115

Electronic Service Requested

Nonprofit Organization

U.S. Postage PAID
Burlington, VT 05401
Permit No. 391

JAY WATSON

In the Lead

Anula Jayasuriya, whose venture capital fund is a pioneer in investing in women's health, thinks it's vital there be increased awareness of the gaps in women's health research and advocacy to "remedy the status quo."